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NUCLEOPHILIC PHOSPHINE ADDITION: EXPLORATION OF NOVEL ALKYNE TRANSFORMATIONS

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NUCLEOPHILIC PHOSPHINE ADDITION: EXPLORATION OF NOVEL ALKYNE TRANSFORMATIONS

A Thesis
Presented to
the Faculty of the Department of Chemistry
Murray State University
Murray, Kentucky

In Partial Fulfillment
of the Requirements for the Degree
of Master of Science in Chemistry

by Brett Matthew Pierce
May 14, 2019
Acknowledgements

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Specifically, Dr. Rachel Whittaker severed as my mentor, my research advisor, and my friend. You have not only taught me how to be an organic chemist and scientist, you have taught me the skills necessary to flourish within a field of work, you have taught me professionalism, and you have taught me how to make something of myself. Your direction and leadership skills are irrefutable, and I have no doubt that you will be successful in whatever you hope to achieve. Starting a research lab from scratch is not the easiest endeavor; however, the skills and knowledge learned from doing so are invaluable. In return, I have always sought to provide effort, enthusiasm, dependability, and most importantly results.

Additionally, I would like to thank all my undergraduate students in our research group that helped the transformation of research into publications and gave me the opportunity to teach someone the same skills I learned throughout my time here. Since that time has witnessed five generations of iPhones, numerous students in our research group have come and gone; however, I would like to say a special thank you to Kane Ferguson.

Lastly, I would like to thank all my family and friends who have helped me, despite me completely falling off the grid. Particularly, my sister Amy, who helped me make this possible through the years of us growing up together. You have been my support since birth, the person I can always rely on, and my best friend.
Abstract

Nucleophilic phosphine catalysis has demonstrated its value in synthetic chemistry by allowing for mild carbon-carbon bond formation. Many phosphine-catalyzed reactions with electron-deficient alkynes have been reported in recent years, leading to an array of valuable products. Stemming from this field of study, phosphines can also be utilized as mild chemoselective reductants for alkynes, resulting in the corresponding alkenes. Herein, a mild, stereoselective, phosphine-mediated partial reduction of alkynes to (E)- and (Z)-alkenes is described. Specifically, a general method for the partial reduction of ynoates to the corresponding (E)- and (Z)-enoate, and ynones to the corresponding (E)-enones has been developed. Furthermore, it has been demonstrated that ynones can stereoselectively arrive at (Z)-enones through the careful examination and tuning of phosphines; however, fully optimized conditions are still being explored.

In addition to this work, a phosphine-catalyzed annulation was investigated, and showed the potential to form dihydro-1,2-oxazines starting from ynones and nitrones. Another redox strategy for carbon-carbon bond formation was also researched, incorporating an iron-catalyst that facilitated hydrogen transfers through an intramolecular process. From this strategy, a three-component, “one-pot” 1,3-amino alcohol synthesis was explored, employing the Mannich reaction and using readily available starting materials.
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1. Introduction

1.1 Nucleophilic Phosphine Catalysis

The chemistry of phosphine is centered on its lone pair of electrons, available to use for bond formation with a variety of electrophilic species. Though functionally and structurally similar to amines, phosphines are generally less basic and more nucleophilic than similarly substituted amines.\(^1\) Soft bases such as phosphines have empty low-energy orbitals, unlike amines, and have a much higher polarizability due to their larger size. Thus, phosphines exhibit enhanced nucleophilicity and will preferentially coordinate with softer electrophiles, drastically diminishing their inherent capabilities to act as bases for hard acids. The relative nucleophilicity of various phosphines has been extensively studied by measuring their reaction rates with a soft electrophile, such as methyl iodide.\(^1,2\) These studies illustrated that triphenylphosphine exhibited weaker nucleophilicity than the more electron-rich trialkylphosphines. Additionally, trialkylphosphines demonstrated nearly a 100-fold increase in nucleophilicity when compared with triethylamine, despite triethylamine being 100-fold more basic.\(^1,2\)

Organophosphorus compounds have been widely employed in synthetic organic chemistry. Phosphonium ylides and zwitterionic species are common intermediates in reactions mediated by phosphines. For example, an isolated zwitterionic species, formed from triethyl and triphenylphosphine with ethylene malononitrile, was accomplished in 1955 by Horner (Scheme 1.1).\(^3\) Huisgen realized the zwitterionic intermediate (Scheme
1.2A) in the reactions of triphenylphosphine and diethyl azodicarboxylate (DEAD). This was later recognized as they key intermediate in the renowned Mitsunobu reaction, a common method for stereochemically inverting chiral alcohols (Scheme 1.2B).\textsuperscript{4,5} Both the Wittig and Mitsunobu reactions utilize these common intermediates, resulting in triphenylphosphine oxide. Since these early and well-known examples, using phosphines as nucleophilic catalysts has become an impactful topic of research.

\textit{Scheme 1.2: The Mitsunobu Reaction}

Nucleophilic phosphine catalysis is generally initiated by the addition of tertiary phosphines to an activated carbon-carbon multiple bond. This addition forms an $\alpha$-carbanion-$\beta$-phosphonium zwitterionic species (Figure 1.1). In 1963, Rauhut and Currier disclosed the first tributylphosphine-catalyzed dimerization of activated alkenes, forming $\alpha$-methylene succinates (Scheme 1.3A).\textsuperscript{6} Around the same time, Winterfeldt reported the first triphenylphosphine-catalyzed annulation, constructing butenolides from dimethyl acetylene dicarboxylate and aldehydes (Scheme 1.3B).\textsuperscript{7} Two years later, the Morita reaction was discovered, in which a zwitterion adds to an aldehyde to eventually arrive at $\alpha$-
hydroxymethylated acrylates using a tributylphosphine catalyst (Scheme 1.3C).  

**Scheme 1.3: Early Phosphine Catalysis Examples**

These novel examples of nucleophilic phosphine catalysis demonstrated an extremely valuable tool for synthetic chemistry by allowing for mild carbon-carbon bond formation. After these seminal studies, reports of nucleophilic phosphines as organocatalysts were relatively sparse. However, recognition of this potential has led to considerable attention in recent years. Because the catalytic behavior and properties of nucleophilic phosphines significantly differ from those of amines, many unique transformations with electron-deficient alkenes, alkynes, and allenes have been reported in recent years. Overall, this growth can be attributed to phosphine catalysis possessing several desirable features: (1) the reactions are highly atom-economical and typically do not produce by-products; (2) the catalytic system is metal-free, permitting it to be performed in bulk (a beneficial feature for pharmaceutical applications); and (3) the specific transformation can be controlled through careful choice of the phosphine catalyst. Additionally, an advantage of nucleophilic phosphine catalysis is that it can often yield complex structural motifs in one step from simple starting materials.
1.2 **Nucleophilic Phosphine Catalysis of Alkynes**

Numerous chemical reactions can occur when activated alkynes are introduced to phosphine catalysts. These reactions can broadly be characterized into two main categories: (1) an alkynyl isomerization to form a conjugated diene; or (2) addition reactions when in the presence of a nucleophile. In the second case, two major reaction pathways can occur: Michael addition or α-umpolung addition. Additionally, annulations can take place, generating a diverse array of carbo- and heterocycles.

1.2.1 **Alkyne Isomerization**

The first detailed study of nucleophilic phosphine addition to an alkyne was published by Trost in 1992 (Scheme 1.4). Trost illustrated the isomerization of activated alkynes to dienes, using triphenylphosphine (PPh₃) as a catalyst. PPh₃ adds to the alkyne, resulting in the zwitterionic species I. After a proton transfer, intermediate II is in resonance with intermediate III, which generates a phosphonium ylide IV through an additional proton transfer. Intermediate IV exists in resonance with intermediate V, and after
another proton transfer, intermediate VI is formed. Lastly, the subsequent elimination of PPh₃ affords the diene VII.

Generally, alkynes activated by adjacent ketones are more reactive than esters, which are more reactive than amides. In order to efficiently isomerize alkynes that exhibited lower reactivity, higher temperatures and acidic additives were used (Scheme 1.5). In the case where both an ynone and ynamide was present, selective isomerization of the ynone occurred, leaving the less reactive ynamide unperturbed (in the absence of acidic additives).

Scheme 1.5: Phosphine-Catalyzed Alkyne Isomerization
The next year, Guo and Lu also reported the phosphine catalyzed isomerization of alkynes, with a focus on the less reactive ynoates and ynamides.\textsuperscript{12} Instead of implementing an acidic additive, Guo and Lu utilized a more nucleophilic phosphine, tributylphosphine.  

*Table 1.1: The Isomerization of Less Reactive Alkynes*

<table>
<thead>
<tr>
<th>Entry</th>
<th>R\textsubscript{1}</th>
<th>R\textsubscript{2}</th>
<th>Time (h)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>\begin{center}![\text{Ynoate Image}]\end{center} &amp; Me</td>
<td>30</td>
<td>89%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>\begin{center}![\text{Ynamide Image}]\end{center} &amp; Et</td>
<td>24</td>
<td>82%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>\begin{center}![\text{Ynenone Image}]\end{center} &amp; Me</td>
<td>24</td>
<td>60%</td>
<td></td>
</tr>
</tbody>
</table>

Ynoates, ynamides, and even ynenones were converted to the desired corresponding dienes or trienes with good yields (Table 1.1). Additionally, without employing an acid additive, the methodology could be effectively applied towards substrates containing acid-sensitive functional groups such as nitriles and acetics. Following up Guo and Lu, Rychnovský established milder conditions for isomerization, featuring phenol as an additive.\textsuperscript{13} This research allowed for a lower temperature and time to efficiently perform the acidic isomerization reaction (Table 1.2).
Table 1.2: Milder Conditions for the Isomerization of Less Reactive Alkynes

<table>
<thead>
<tr>
<th>Entry</th>
<th>R₁</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(CH₂)₃CH₃</td>
<td>70%</td>
</tr>
<tr>
<td>2</td>
<td>Me-OTBS</td>
<td>75%</td>
</tr>
<tr>
<td>3</td>
<td>CH₃CH₃</td>
<td>88%</td>
</tr>
</tbody>
</table>

1.2.2 Michael Addition of Alkynes with Nucleophiles

When a nucleophile is added to an activated alkyne and phosphine, transformations beyond isomerization can take place. Phosphine-catalyzed Michael reactions (addition of a nucleophile to the β-position) have been well established (Scheme 1.6). Generation of the zwitterion I is as previously shown. The zwitterion then deprotonates the nucleophile, and Michael addition occurs, generating intermediate III.
After a subsequent proton transfer and phosphine elimination of the Michael adduct, the alkene product is afforded.

The first phosphine-catalyzed alkynyl Michael addition was established in 1993 by Inanaga.\textsuperscript{14} This reaction utilized alcohol and thiol pronucleophiles to add to methyl propiolate. Primary alcohols afforded excellent yields of the Michael adducts, and exclusively gave the (E)-isomers (Table 1.3). When a secondary alcohol was analyzed in this system however, yield was drastically lowered, and no reaction occurred at all when a tertiary alcohol was used. Furthermore, primary thiols were as efficient as primary alcohols when investigated within the same system.

\textit{Table 1.3: Initial Phosphine-Catalyzed Alkynyl Michael Addition}

<table>
<thead>
<tr>
<th>Entry</th>
<th>H-Nu</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCH=CHOH</td>
<td>90%</td>
</tr>
<tr>
<td>2</td>
<td>O{\text{cyclpentanediol}}</td>
<td>&gt;98%</td>
</tr>
<tr>
<td>3</td>
<td>H_{3}C{\text{H}<em>{2}C}</em>{3}\text{OH}</td>
<td>14%</td>
</tr>
<tr>
<td>4</td>
<td>n-C_{17}H_{35}SH</td>
<td>95%</td>
</tr>
</tbody>
</table>

Other pronucleophiles for Michael addition have also been investigated. $\alpha$-Hydroxyenones, haloalcohols, hydroxypyridines, oximes, phthalimides, pyrazoles, and salicylaldehydes are all functionally capable of undergoing phosphine-catalyzed Michael reactions with alkynes.\textsuperscript{15-21} Recently, Zhang and Li reported a phosphine-catalyzed stereoselective formation of 1,3-butadiene derivatives from the addition of various aryl alcohols and carboxylic acids to yne-enones (Scheme 1.7).\textsuperscript{22} Both aryl and alkyl yne-enones underwent the reaction to form the corresponding adducts in moderate to good yields, stereoselectively forming the (E)-isomers.
Annulations were not reported until 1998, when Yavari reported a Michael-lactonization process. More notably, Fan and Kwon demonstrated an annulation strategy for generating complex structural motifs through a phosphine- and palladium-catalyzed tandem Michael-Heck reaction (Table 1.4). An exceptional characteristic of this reaction is the dual-reactivity exhibited by PPh₃; initially, it acted as a nucleophilic catalyst, then functioned as a ligand for palladium. This bi-catalytic system was capable of constructing phthalans in good to high yields using o-iodobenzyl alcohols as the pronucleophile (Table 1.4). Additionally, (Z)-isomers were formed predominantly with moderate to good stereoselectivity for most substrates. In 2015, Kwon and Fan extended this reaction system to prepare indanone derivatives. Various o-iodobenzylmalonates or o-iodobenzylacetates underwent PPh₃-catalyzed Michael addition with electrophilic alkynes, then were subjected to Pd(OAc)₂, generating the indanone products. This research

Scheme 1.7: Phosphine-Catalyzed Stereoselective Michael Addition

Table 1.4: Phosphine/Palladium-Catalyzed Tandem Michael-Heck Reaction
exemplified the synthetic applications of this Michael-Heck process by preparing a nonsteroidal anti-inflammatory drug Sulindac (Scheme 1.8).

Scheme 1.8: Sulindac Synthesis via Michael-Heck Process

All previous examples, in which one equivalent of pronucleophile reacts with one equivalent of an activated alkyne, ultimately forms a two-molecule adduct. However, dinucleophile and dipropiolate systems, resulting in polymers, have proven to be mild and efficient as well (Scheme 1.9).27-28 These studies showed that although a diol was polymerized without stereoselectivity issues ((E)-isomer only), a dithiol produced a polymer containing a mixture of (E)- and (Z)-isomers, though the (Z)-isomer was slightly favored. Most notably, this method has been applied towards generating novel dithioacetal polymers.
1.2.3 α-Umpolung Addition of Nucleophiles to Alkynes

Converse to Michael addition, addition of pronucleophiles to the α-position of the alkyne can also occur. This reverse reactivity pattern occurs when an alkyne lacks a γ-proton and the nucleophilic addition of the phosphine occurs through an α-umpolung addition instead (Scheme 1.10). Once the typical phosphine addition occurs to give the vinyl phosphonium enoate I, the α-umpolung addition of the nucleophile forms the ylide III. A subsequent proton transfer and the elimination of PPh₃ affords the acrylate IV. This discovery was first made by Trost in 1997, employing a phthalimide and a sulfonamide as pronucleophiles, allowing for the formation of α-dehydroamino acids (Table 1.5).
Scheme 1.10: Proposed Mechanism for Phosphine-Catalyzed α-Umpolung Addition

Table 1.5: α-Umpolung Addition of a Phthalimide and a Sulfonamide
In 2003, Tomita (Scheme 1.11A) reported a phosphine-catalyzed intramolecular cycloaddition of stereoisomeric yne-diones to form bicyclic ketones, and in 2010, Fu (Scheme 1.11B) reported a phosphine-catalyzed intramolecular cycloaddition of yne-diones to form diquinanes.\textsuperscript{30,31} In 2012, Huang realized the intermolecular version of a phosphine-catalyzed cycloaddition, and also resolved the problems of unsatisfactory yields and restricted substrate scope previously hindering this research (Scheme 1.12).\textsuperscript{32}

In cycloaddition processes, ynones possess characteristics of three-membered synthons (Figure 1.2).

In 2016, Huang reported that when ynones reacted with other three-membered synthons in the presence of a phosphine catalyst, a [3 + 3] annulation can occur (Scheme 1.13).\textsuperscript{33} After the nucleophilic addition of PPh\textsubscript{3} to an ynone, the enolate nucleophile then adds to the electrophilic azomethine imine generating intermediate \textbf{III}. This intermediate undergoes an intermolecular $\alpha$-umpolung addition to achieve intermediate \textbf{IV}.

\textit{Scheme 1.11: Phosphine-Catalyzed Annulations via $\alpha$-Umpolung Addition}

\textit{Scheme 1.12: Intermolecular $\alpha$-Umpolung Addition}

\textit{Figure 1.2: Ynones as 3-Membered Synthons}
An additional proton transfer and subsequent elimination of PPh$_3$ then affords the cyclic product VI.

*Scheme 1.13: Proposed Mechanism of Novel [3 + 3] Annulation*
1.3 Phosphine-Mediated Reduction of Alkynes

In addition to isomerization and carbon-carbon bond forming reactions, tertiary phosphines can also be utilized as mild chemoselective reductants for alkynyl carbonyl species. This was first realized in the 1960s when PPh$_3$ was refluxed in THF with dimethyl acetylenedicarboxylate. Water was used as a co-solvent, yielding triphenylphosphine oxide and dimethyl fumarate products (Scheme 1.14). The reaction scope was marginally expanded and yielded predominantly (E)-olefins in moderate yields (Table 1.6). It should be further noted that this reduction process is phosphine-mediated, not catalyzed; triphenylphosphine oxide is produced as a stoichiometric by-product.

In 1993, Larpent and Meignan demonstrated that an aqueous solution containing a water-soluble sulfonated phosphine could reduce alkynyl carbonyls, resulting in a mixture of (E)- and (Z)-alkenes (Scheme 1.15). The two step proposal begins with the hydrolysis of (E)- and (Z)-vinylphosphonium salts leading to some diasteromeric mixture of (E)- and (Z)-olefins.
Secondly, a catalytic (Z)- to (E)-isomerization of the resulting olefins can occur due to the slight excess in initial phosphine.

Interestingly, the isomerization, catalyzed by the phosphine, did not involve a protonation step, as no incorporation of deuterium was found for the product in the presence of D$_2$O, and no alkane was observed. As such, a mechanism that is known for other nucleophiles was proposed for this system (Scheme 1.16). This proposed mechanism involves the phosphine nucleophilically adding to the (Z)-olefin to form a zwitterionic $sp^3$-hybridized intermediate that has free rotation. The subsequent elimination of the phosphine then affords the more thermodynamically favored (E)-olefin.

Scheme 1.16: Proposed Mechanism for the (Z)- to (E)-Alkene Isomerization
1.4 Phosphine-Mediated Reduction of Other α,β-Unsaturated Carbonyls

In 2003, Giri reported a phosphine-mediated reduction of maleimides in methanol. The reduction of these α,β-unsaturated carbonyls begins with the nucleophilic addition of triphenylphosphine to the maleimide I (Scheme 1.17). This is followed by the formation of intermediate II via protonation. After the elimination of triphenylphosphine oxide, the succinimide (III) is yielded. The maleimides utilized for this system must be protected to avoid nucleophilic addition by the amine. Derivatized succinimides can be produced in moderate to good yields, although the substrate scope is very limited.

Scheme 1.17: Phosphine-Mediated Reduction of Maleimides

To further expand the scope of phosphine-mediated reduction of α,β-unsaturated carbonyls, Shi showed that a stoichiometric amount of trimethylphosphine could efficiently reduce specific isatin derivatives (Table 1.7). Both ketones and esters could act as activating groups. Lower yields were obtained when a trifluoromethyl group was implemented at C7 (entry 5), and when an electron-withdrawing Boc group was utilized instead of

<table>
<thead>
<tr>
<th>Entry</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et</td>
<td>H</td>
<td>Bn</td>
<td>99%</td>
</tr>
<tr>
<td>2</td>
<td>OEt</td>
<td>H</td>
<td>Bn</td>
<td>99%</td>
</tr>
<tr>
<td>3</td>
<td>OEt</td>
<td>5-Me</td>
<td>Bn</td>
<td>99%</td>
</tr>
<tr>
<td>4</td>
<td>OEt</td>
<td>H</td>
<td>H</td>
<td>99%</td>
</tr>
<tr>
<td>5</td>
<td>OEt</td>
<td>7-CF₃</td>
<td>Bn</td>
<td>16%</td>
</tr>
<tr>
<td>6</td>
<td>OEt</td>
<td>H</td>
<td>Boc</td>
<td>53%</td>
</tr>
</tbody>
</table>
the electron-donating benzyl protecting group (entry 6). In the proposed reaction mechanism, nucleophilic addition of the phosphine generates the phosphonium enolate I, which is subsequently protonated by water (Scheme 1.18). Keto-enol tautomerization then affords intermediate III, and oxidation of trimethylphosphine, followed by elimination of trimethylphosphine oxide, gives the 2-oxindole derivative.

Scheme 1.18: Proposed Mechanism for the Phosphine-Mediated Reduction of Isatin Derivatives

1.5 The Electronic and Steric Effects of Phosphines

Phosphines (PR₃) have showed immense value as ligands in organometallic catalysis because they allow for the tuning of the metal catalysts in terms of both steric and electronic factors by means of varying the R groups.³⁹ Phosphine ligand properties have primarily been studied via the Tolman cone angle (θ) or an electronic parameter (ν).⁴⁰ Prior to the 1970s, most phosphorous compounds were evaluated simply in terms of electronic effects.⁴¹ Since that time, numerous papers have established that steric effects are generally at least as important as electronic effects, and can even dominate in many cases. Moreover, steric effects can have

Figure 1.3: Steric Influences on the Electronics of Phosphines
implications on the electronics of the phosphorous compound and vice-versa. For example, increasing the angles between substituents will decrease the percentage of sigma bonding character in the phosphorus lone pair (Figure 1.3). Alternatively, varying substituent electronics can also affect bond distances and angles between each R group. These tunable phosphine characteristics are distinguished through the parameters \( \nu \) and \( \theta \) and are well defined for targeting the design of a new catalyst or improving an existing one. Utilizing these known properties, the relative differences in electronic and steric character between phosphines could potentially lead to further insight of phosphine-catalyzed systems.

### 1.5.1 The Electronic Parameter \( \nu \)

Phosphorous ligands can be ranked in terms of nucleophilicity based on their electronics when coordinated to transition metal carbonyls. This is due to changes in CO vibrational stretching frequencies.\(^{42} \) For example, in a Ni(CO)\(_3\)L system the relative electronic contribution of the ligand L can be determined by adding each individual phosphine substituent’s contribution to \( \nu \) (Table 1.8). Furthermore, it is found that parameter \( \nu \) is not affected by steric effects of the transition metal carbonyl, as suggested from almost identical values of \( \nu \) for entries 1 and 2.

**Table 1.8: Values of \( \nu \) (cm\(^{-1}\)) for Selected Phosphines**

<table>
<thead>
<tr>
<th>Entry</th>
<th>( \chi_i )</th>
<th>( \nu ) (cm(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{PX}_2X_3 )</td>
<td>( \nu = 2056.1 + \sum_{i=1}^{3} \chi_i )</td>
<td>( 2056.1 )</td>
</tr>
</tbody>
</table>

Phosphines that are more nucleophilic increase the electron density at the metal center resulting in a strong back-donation of electron density to the \( \pi^* \) orbital of CO (Figure 1.4). This effect causes the lowering of the CO stretching frequency; as such, a better electron donor on PR\(_3\)
will lead to a greater decrease in the CO frequency. Moreover, the increasing nucleophilicity of alkyl phosphines in entries 3-7 is also partially due to alkyl-alkyl repulsion. Bulkier phosphines, exhibiting a relatively larger degree of torsional strain, decreases the sigma character in the lone pair. This is due to the larger substituents on the phosphine forcing open the $s$-$sp$ orbital overlap, increasing the electronic repulsion between the molecules of the phosphine.

### 1.5.2 The Steric Parameter $\theta$

The ligand cone angle $\theta$ was formally introduced after it was evident that phosphorous ligands had the ability to compete for coordination positions on Ni(0) that could not be explained through electronic properties. This steric effect of phosphines was quantified by Tolman in 1977, and ($\theta$) is known as the Tolman cone angle (Table 1.9). The Tolman cone angle is defined as the apex angle of a cylindrical cone centered 2.28 Å from the center of the phosphorus atom, barely touching the van der Waals radii of the outermost atoms of the substituents on phosphine (Figure 1.5). This steric approximation has become very useful due to the steric profile of phosphines significantly impacting the degree of control over the outcome of an organometallic-mediated or catalyzed reaction. For example, this subtle balancing act of matching a
suitable phosphine for an efficient reaction was reported in a phosphine-catalyzed disulfide metathesis (Table 1.10). As the relative phosphine cone angle decreased, significant improvement was found in the equilibrated yield. Additionally, phosphines in entries 1-4 decrease in nucleophilicity, further illustrating the impact phosphine sterics applied within this disulfide metathesis system. Despite being the least nucleophilic phosphine examined, the sterically less hindered PPh₃ proved to substantially reduce the time required to reach equilibrium (Entry 4). Metathesis equilibrium was ultimately reached in 8 minutes using the sterically least hindered, most nucleophilic phosphine, P(NEt₂)₃ (Entry 5).

\[
\text{Table 1.10: Phosphine-Catalyzed Disulfide Metathesis}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat.</th>
<th>Cone Angle</th>
<th>Time (h)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>P(BiPh)Cy₂</td>
<td>183°</td>
<td>68</td>
<td>45% (A), 45% (B), 10% (C)</td>
</tr>
<tr>
<td>2</td>
<td>PCy₂Ph</td>
<td>164°</td>
<td>68</td>
<td>27% (A), 27% (B), 46% (C)</td>
</tr>
<tr>
<td>3</td>
<td>PCyPh₂</td>
<td>151°</td>
<td>68</td>
<td>26% (A), 26% (B), 48% (C)</td>
</tr>
<tr>
<td>4</td>
<td>PPh₃</td>
<td>145°</td>
<td>44</td>
<td>23.5% (A), 23.5% (B), 53% (C)</td>
</tr>
<tr>
<td>5</td>
<td>P(NEt₂)₃</td>
<td>108°</td>
<td>0.13</td>
<td>22% (A), 22% (B), 56% (C)</td>
</tr>
</tbody>
</table>

1.5.3 The Stereoelectronic Profile of Phosphines

The stereoelectronic profile for phosphine ligands have been previously estimated using the combined approach of quantum mechanics and molecular mechanics. The computational measure of the total electronic effect (E_{eff}) and steric effect (S_{eff}) provides a measurement of the electrostatic potential minimum (V_{min}) of a PR₃ ligand at the phosphorus lone pair. Additionally, the difference between the V_{min} of unsubstituted PH₃ and the V_{min} of PR₃ is defined as E_{eff} + S_{eff}; therefore, the relative nucleophilicity of a phosphine can be evaluated with steric influences accounted for (Figure 1.6). For example, PPh₃ has a calculated V_{min} value of -34.07 (kcal/mol) compared to the calculated V_{min} value
of -28.22 (kcal/mol) for PH₃; therefore, the relative nucleophilicity of PPh₃ incorporating steric contributions equals 5.85 (kcal/mol).

Additionally, the changes in the bulkiness of R groups can potentially alter the character of the sp³-hybridized lone pair orbital of the phosphorus atom, in turn leading to a corresponding increase or decrease in the negative character of the \( V_{\min} \) of the lone pair. A lower value for \( V_{\min} \) than for \( V_{\min}(\text{PH}_3) \) indicates the phosphine ligand is electron-donating, while electron-withdrawing ligand exhibits a \( V_{\min} \) greater than \( V_{\min}(\text{PH}_3) \) (Table 1.11). For comparison, the reduced electron-donating behavior of aryl phosphines such as PPh₃ is illustrated from the lower \( V_{\min} \) value of -34.07 kcal/mol, compared to the behavior of alkyl phosphines such as PMe₃ with a \( V_{\min} \) value of -43.55 kcal/mol. Overall, the \( V_{\min} \) values are more influenced by the nature of the R group than by the steric bulkiness of the R group.

**Table 1.11: \( V_{\min} \) and \( E_{\text{eff}} + S_{\text{eff}} \) values for PR₃**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand (PR₃)</th>
<th>( V_{\min} ) (kcal/mol)</th>
<th>( E_{\text{eff}} + S_{\text{eff}} ) (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>P(CF₃)₃</td>
<td>-5.95</td>
<td>-22.27</td>
</tr>
<tr>
<td>2</td>
<td>P(2-C₆H₄F)₃</td>
<td>-27.77</td>
<td>-0.45</td>
</tr>
<tr>
<td>3</td>
<td>PH₃</td>
<td>-28.22</td>
<td>0.00</td>
</tr>
<tr>
<td>4</td>
<td>PH₂Ph</td>
<td>-31.05</td>
<td>2.83</td>
</tr>
<tr>
<td>5</td>
<td>PPh₃</td>
<td>-34.07</td>
<td>5.85</td>
</tr>
<tr>
<td>6</td>
<td>PMePh₂</td>
<td>-36.76</td>
<td>8.54</td>
</tr>
<tr>
<td>7</td>
<td>PETPh₂</td>
<td>-37.23</td>
<td>9.01</td>
</tr>
<tr>
<td>8</td>
<td>P(t-Bu)Ph₂</td>
<td>-38.86</td>
<td>10.64</td>
</tr>
<tr>
<td>9</td>
<td>PMe₂Ph</td>
<td>-40.41</td>
<td>12.19</td>
</tr>
<tr>
<td>10</td>
<td>PMe₃</td>
<td>-43.02</td>
<td>14.80</td>
</tr>
<tr>
<td>11</td>
<td>PET₃</td>
<td>-43.55</td>
<td>15.33</td>
</tr>
<tr>
<td>12</td>
<td>P(i-Pr)₃</td>
<td>-44.18</td>
<td>15.96</td>
</tr>
<tr>
<td>13</td>
<td>P(t-Bu)₃</td>
<td>-44.90</td>
<td>16.68</td>
</tr>
<tr>
<td>14</td>
<td>PCy₃</td>
<td>-44.99</td>
<td>16.77</td>
</tr>
</tbody>
</table>
2. Phosphine-Mediated Partial Reduction of Alkynes to Form Both \((E)\)- and \((Z)\)-Alkenes

2.1 Project Scope

Although phosphine-mediated partial reduction of alkynes has been reported\(^{34-36}\), the chemistry remains largely unexplored and contains few examples. Due to the mild nature and functional group tolerance of the reduction, an in-depth exploration of optimal conditions and substrate scope would be an important development. Based on these early reports, it was hypothesized that a method could be made that was more general for a wide variety of alkynyl carbonyls. Additionally, since the \((E)/(Z)\)-isomerization of alkenes by nucleophilic phosphine addition had been established, it was hypothesized that by tuning the reaction conditions, the stereoselective formation of both \((Z)\)- and \((E)\)-alkenes could be achieved.

To examine our hypothesis, alkynyl ester \textbf{2.1a} was chosen (1) because it would be intermediate in reactivity towards the phosphine between ketones and amides, and (2) in order to avoid the possibility of 1,3-hydrogen transfer, which could interfere with the reactivity or selectivity of the reaction (Table 2.1).
Table 2.1: Reaction Condition Optimization Table

<table>
<thead>
<tr>
<th>Entry</th>
<th>PPh₃ (Equiv.)</th>
<th>H₂O (Equiv.)</th>
<th>Solvent</th>
<th>Additive</th>
<th>Yield (E:Z)²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.8</td>
<td>55</td>
<td>EtOH</td>
<td>-</td>
<td>43% (58:42)</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>55</td>
<td>EtOH</td>
<td>-</td>
<td>51% (69:31)</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>55</td>
<td>EtOH</td>
<td>-</td>
<td>42% (70:30)</td>
</tr>
<tr>
<td>4</td>
<td>1.5</td>
<td>25</td>
<td>THF</td>
<td>-</td>
<td>46% (10:90)</td>
</tr>
<tr>
<td>5</td>
<td>1.5</td>
<td>25</td>
<td>Toluene</td>
<td>-</td>
<td>&lt;5% (6:94)</td>
</tr>
<tr>
<td>6</td>
<td>1.5</td>
<td>25</td>
<td>DCE</td>
<td>-</td>
<td>30% (12:88)</td>
</tr>
<tr>
<td>7</td>
<td>1.5</td>
<td>40</td>
<td>THF</td>
<td>-</td>
<td>68%* (15:85)</td>
</tr>
<tr>
<td>8</td>
<td>1.5</td>
<td>100</td>
<td>THF</td>
<td>-</td>
<td>45% (17:83)</td>
</tr>
<tr>
<td>9</td>
<td>1.5</td>
<td>25</td>
<td>THF</td>
<td>1.5 equiv PhCO₂H</td>
<td>91%* (89:11)</td>
</tr>
<tr>
<td>10</td>
<td>1.5</td>
<td>40</td>
<td>THF</td>
<td>1 equiv. ZnCl₂</td>
<td>44% (68:32)</td>
</tr>
</tbody>
</table>

*The reactions were run with ynoate 2.1a (0.10 mmol). *²Yield and (E):Z ratio were determined via ¹H NMR using 1,3,5-trimethoxy benzene as the internal standard.

First, using ethanol as the solvent, the equivalents of triphenylphosphine needed were explored. A greater than a stoichiometric amount (1.5 equivalents) was found to be optimal for increased yield, though the (E):(Z) selectivity was poor (Entry 2). Next, solvent effects were explored and these were found to play a crucial role in the diastereoselectivity. By switching from ethanol to THF, the selectivity was inverted to greatly favor the (Z)-alkene (Entry 4). Use of other solvents showed decreased yield, likely due to lack of miscibility with water (Entries 5 and 6). Slightly increasing the amount of water to 40 equivalents increased the yield, while only marginally reducing the selectivity for the (Z)-enoate (Entry 7).

Satisfied with the formation of (Z)-alkenes, focus was returned to the (E)-isomer. It was hypothesized that an acidic additive could help the stereoselectivity of the reaction due to the enhanced substrate electrophilicity. Indeed, the addition of benzoic acid was found to invert the stereoselectivity once again and led to the (E)-enoate in high yield and
with high diastereoselectivity (Entry 9). Addition of a non-protic Lewis acid, such as ZnCl₂, did not show any improvement over benzoic acid (Entry 10).

### 2.2 Substrate Scope

With both sets of optimized conditions in hand, the substrate scope for (E)-enoates was explored (Table 2.2). First, electronic effects were explored on the aryl ring (2.2b-2.2d). The electron-donating methoxy group 2.1b gave excellent yield and (E)-selectivity of the alkene. Electron withdrawing groups such as chloro- and nitro- (2.1c, 2.1d) also gave excellent yield, though the (E)- to (Z)- ratio was slightly diminished. Notably, no reduction of the nitro group was observed. To test if steric bulk would be tolerated, o-tolyl- substrate 2.1e was subjected to the reaction conditions. The yield was lowered (68%), while also severely reducing (and slightly inverting) the diastereoselectivity ((E):(Z), 42:58).

**Table 2.2: The Reduction of Ynoates to Form (E)-Enoates**

<table>
<thead>
<tr>
<th>2.1a-h</th>
<th>2.2a-h</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Reaction Scheme" /></td>
<td><img src="image" alt="Reaction Scheme" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>R</th>
<th>1.5 equiv. PPh₃</th>
<th>THF, 24 h, 65°C</th>
<th>25 equiv. H₂O</th>
<th>R'</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>Ph</td>
<td><img src="image" alt="" /></td>
<td></td>
</tr>
<tr>
<td>MeO</td>
<td>MeO</td>
<td>MeO</td>
<td><img src="image" alt="" /></td>
<td></td>
</tr>
<tr>
<td>Cl</td>
<td>Cl</td>
<td>Cl</td>
<td><img src="image" alt="" /></td>
<td></td>
</tr>
<tr>
<td>O₂N</td>
<td>O₂N</td>
<td>O₂N</td>
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<tr>
<td><img src="image" alt="" /></td>
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<td><img src="image" alt="" /></td>
<td><img src="image" alt="" /></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(%Yield (E:Z))</th>
<th>2.2a (91% (89:11))</th>
<th>2.2b (84% (92:8))</th>
<th>2.2c (83% (75:25))</th>
<th>2.2d (90% (78:22))</th>
<th>2.2e (68% (42:58))</th>
<th>2.2f (no rxn)</th>
<th>2.2g (no rxn)</th>
<th>2.2h (no rxn)</th>
</tr>
</thead>
</table>
Aliphatic alkynes were also of interest; unfortunately, one inherent limitation of the alkyne scope was that substrates needed to be blocked alpha to the alkyne to avoid the competing phosphine-catalyzed isomerization to the conjugated diene. To avoid a phosphine-catalyzed isomerization, the tertiary, aliphatic tert-butyl alkyne 2.1f was used. Unfortunately, it showed no reaction under the standard conditions due to its bulkiness. Similarly, the aliphatic alkyne 2.2g, and the bulky aryl alkyne 2.2h resulted in no reaction.

Ynoates 2.1a-h were also subjected to the (Z)-enoate-forming optimized conditions (Table 2.3). First, substituent effects were explored on the aryl ring (2.2b-2.2e). For p-OMe and p-Cl groups, the (Z)-enoate was favoured and in good yields. However, for the strongly electron-withdrawing p-NO₂ group, the (E)-enoate was still favoured ((E):(Z), 72:28), due to the increased electrophilicity of the alkene, though the overall yield was slightly higher (87%) compared with other substrates. To test if steric bulk would be tolerated, the o-tolyl (2.1e) substrate was subjected to the reaction conditions. The addition of steric bulk did not affect yield greatly, but showed extremely high diastereoselectivity for the (Z)-isomer ((E):(Z), 2:98) (vide infra).

Table 2.3: The Reduction of Ynoates to Form (Z)-Enoates

<table>
<thead>
<tr>
<th>R</th>
<th>1.5 equiv. PPh₃</th>
<th>40 equiv. H₂O</th>
<th>THF, 24 h, 65°C</th>
<th>%Yield (E:Z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>2.3a (68% (15:85))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OMe</td>
<td>2.3b (77% (22:78))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cl</td>
<td>2.3c (80% (12:88))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NO₂</td>
<td>2.3d (87% (72:28))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cl</td>
<td>2.3e (69% (2:98))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NO₂</td>
<td>2.3h (no rxn)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>2.3f (no rxn)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OMe</td>
<td>2.3g (no rxn)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
As for the (Z)-enoates, the bulky alkynes 2.1f, 2.1g, and 2.1h showed no reactivity to the reaction conditions.

In addition to esters, other alkynyl carbonyls were also examined (Table 2.4). First, several ketones were explored (2.4a-e). Both aromatic and aliphatic ketones were well tolerated and almost exclusively favoured the formation of (E)-enones, regardless of the reaction conditions used (substrates showed similar yields using either set of conditions (68-91%)). This is presumed to be the result of the increased reactivity of ketones towards nucleophilic attack by the phosphine when compared to esters. An amide was also subjected to the reaction conditions (2.4f). As expected, the morpholino amide’s lowered reactivity towards nucleophilic addition resulted in slightly decreased yield (53%), but (E)-selectivity was still high ((E):(Z), 95:5). Finally, aldehyde 2.4g was found to give the product in 87% yield and with excellent diastereoselectivity ((E):(Z), >99:1).

Table 2.4: The Reduction of Ynones to Form (E)-Enones

| 2.4a-g | 1.5 equiv. PPh₃  
| 1.5 equiv. PhCO₂H  
| 25 equiv. H₂O  
| THF, 24 h, 65°C  
| 2.5a-g |

<table>
<thead>
<tr>
<th>(%Yield (E:Z))</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5a (90% (&gt;99:1))</td>
</tr>
<tr>
<td>2.5b (68% (&gt;99:1))</td>
</tr>
<tr>
<td>2.5c (83% (&gt;99:1))</td>
</tr>
<tr>
<td>2.5d (75% (&gt;99:1))</td>
</tr>
<tr>
<td>2.5e (91% (98:2))</td>
</tr>
<tr>
<td>2.5f (53% (95:5))</td>
</tr>
<tr>
<td>2.5g (87% (&gt;99:1))</td>
</tr>
</tbody>
</table>
2.3 Proposed Reaction Mechanism

Encouraged by the reaction scope, and in order to better understand the mechanism and diastereoselectivity, the following reaction screens were performed (Scheme 2.1). First, 2.1a was subjected to both the (E)- and (Z)-conditions using deuterated water (Scheme 2.1A). $^1$H NMR analysis of both 2.2a-D and 2.3a-D showed deuterium incorporation at both alkene positions with similar (E):(Z) ratios as with water. Next, the more sterically demanding PPh$_2$(o-tolyl) was used as the phosphine in the (E)-enoate reaction (Scheme 2.1B). This led to a slight preference for the (Z)-isomer, though the diastereoselectivity was greatly reduced ((E):(Z), 41:59, compared with 89:11 under the standard conditions). Interestingly, the yield was not reduced under the bulky phosphine conditions.

Finally, pure samples of the (Z)-isomer were subjected to either PPh$_3$, benzoic acid, or both for one hour under the standard
conditions (Scheme 2.1C). With only PPh₃ present, the diastereomeric purity was slightly degraded ((E):(Z), 12:88). This is in agreement with previous mechanistic studies, albeit in water, by Larpent and Meignan. Without PPh₃, but in the presence of benzoic acid, essentially no isomerization was observed after 1 hour. With both PPh₃ and benzoic acid present, however, it was found that the pure (Z)-isomer had isomerized to give a 50:50 (E):(Z) mixture after 1 hour. This supports the theory that the benzoic acid additive is facilitating the (Z) to (E) isomerization catalyzed by PPh₃, though its exact role is still under investigation.

From the results of these experiments, the following mechanism was proposed (Scheme 2.2). First, the phosphine can nucleophilically add to the alkyne. This results in phosphonium zwitterionic intermediate I that can be protonated by either water or benzoic acid (if present in the reaction conditions). The resulting hydroxide can then attack the phosphonium II, which after collapse can give the alkene and triphenylphosphine oxide (confirmed via ³¹P NMR spectroscopy). This results in a mixture of (Z)- and (E)-alkenes, although the exact diastereomeric ratio depends on the water content of the reaction.

Scheme 2.2: Proposed Mechanism

![Scheme 2.2: Proposed Mechanism](image)

After the initial product formation, the (Z)-isomer can further undergo a phosphine-catalyzed isomerization (Scheme 2.3). Larpent and Meignan’s mechanistic studies
suggested this (Z)- to (E)- isomerization could occur in the presence of excess phosphine, where the phosphine adds into the (Z)-alkene to form a zwitterionic intermediate that could undergo free rotation (Scheme 2.4).\textsuperscript{33-34} Subsequent elimination of the phosphine led to the formation of the more thermodynamically-favored (E)-alkene. This second phosphine addition to the $sp^2$ carbon is more sensitive to sterics, as evidenced by the diastereoselectivity of the bulky o-tolyl ester 2.1e. Not only is the yield of this substrate slightly reduced, the reaction exhibits a preference for the (Z)-enoate, even under (E)-forming conditions. This steric effect is also evidenced when a bulkier phosphine reagent was utilized, leading to a slight excess of the (Z)-isomer of the standard substrate.

\textit{Scheme 2.3: Mechanism for the (Z)- to (E)-Alkene Isomerization}

Additionally, this isomerization is proposed to not go through a protonation step from water (or other proton sources); additionally, no over reduction to the alkane was observed. This is further supported by the isomerization control reactions (Scheme 2.1), where the isomerization takes place in the absence of a proton source. Benzoic acid does seem to play a crucial role in the isomerization step, however (Scheme 2.1C). Though its exact function is still being examined, benzoic acid is hypothesized to be playing a stabilizing role to the zwitterionic intermediate. The addition of a non-protic Lewis acid also results in an excess of the (E)-product, further supporting a lack of protonation during
this transformation (Table 2.1, Entry 10). Further studies are ongoing to more fully understand the exact role of the acid additive.

2.4 Conclusions

A metal-free reduction of ynoates and other alkynyl carbonyls was reported. Tuning of the reaction acidity gave (E)- and (Z)-alkenes selectively and in good to high yields. Other functional groups were not reduced under these chemoselective conditions. Further studies to make this method catalytic in phosphine are ongoing.

2.5 Experimental Section

2.5.1 General

Air and moisture sensitive reactions were carried out in flame-dried glassware under nitrogen. All other reactions were set-up in 8 mL oven-dried glass vials under an ambient atmosphere. Unless otherwise indicated, reagents and materials were obtained from commercial suppliers and used without further purification. Analytical TLC was performed with 0.25 mm silica gel F plates with a 254 nm indicator. Purification of products was achieved by column chromatography on Sorbtech silica gel (40-60 µm), with the indicated solvents.

NMR spectra were measured on a JEOL 400 MHz (ECS-400) Nuclear Magnetic Resonance spectrometer. For CDCl₃ solutions the chemical shifts are reported as parts per million (ppm) referenced to residual protium or carbon of the solvents; CDCl₃ δ ¹H (7.26 ppm) and CDCl₃ δ ¹³C (77.0 ppm). Coupling constants are reported in Hertz (Hz). Characterization data for ¹H-NMR spectra are reported as followed: chemical shift (ppm, s = singlet, d = doublet, dd = doublet of doublets, t = triplet, td = triplet of doublets, q =
quartet, m = multiplet), and integration. Infrared spectra were recorded on a Perkin Elmer FTIR Spectrum II spectrometer, and are reported in wavenumber (cm$^{-1}$) and relative intensity (br = broad, vw = very weak, w = weak, s = strong, vs = very strong, sh = shoulder).

### 2.5.2 Abbreviations

$\text{PPh}_3$ = triphenylphosphine; THF = tetrahydrofuran; DCM = dichloromethane;

EtOAc = ethyl acetate; $n$-BuLi = $n$-butyllithium; TEA = trimethylamine;

DMF = dimethylformamide; Et$_2$O = diethyl ether

### 2.5.3 Experimental Procedures

**General Procedure 1: Preparation of Ynoate Substrates (2.1a and 2.1f):**

![Chemical Reaction]

Procedure adapted from the literature.$^{45}$ Added to a flame-dried Schlenk flask, a solution of the corresponding terminal alkyne (1.0 equiv.) and dry THF (0.25 M) was cooled to 0°C under nitrogen. $n$-BuLi (1.1 equiv.) was added dropwise, and the reaction solution was stirred for 1 hr at this temperature. Ethyl chloroformate (1.5 equiv.) was added dropwise, and the reaction was allowed to warm to rt. The reaction solution was quenched with DI water after 3 hr, extracted with EtOAc, and dried over MgSO$_4$ to afford the crude product. The solvent was removed under reduced pressure, and the crude product was purified via column chromatography on silica gel with hexanes/EtOAc and concentrated to afford the ynoate compound.
Ynoate substrates 2.1a and 2.1f are known compounds from the literature.\textsuperscript{46,47}

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {\includegraphics[width=0.5\textwidth]{2.1a}};
\end{tikzpicture}
\end{center}

**Ethyl 3-phenylpropionate (2.1a)\textsuperscript{46}:** Product isolated as a yellow oil (624.2 mg, 3.58 mmol, 73\%). \textsuperscript{1}H-NMR (400MHz, CDCl\textsubscript{3}) \(\delta 7.58-7.56 (m, 2H), 7.45-7.41 (m, 1H), 7.37-7.33 (m, 2H), 4.31-4.26 (q, J = 8 Hz, 2H), 1.36-1.32 (t, J = 8 Hz, 3H). \) IR (cm\textsuperscript{-1}): 2235.0 (sh), 2209.5, 1703.6 (vs), 1490.2 (w), 1444.6 (w), 1390.2 (vw), 1366.7, 1282.5 (vs), 1187.9 (vs), 1171.5 (sh), 1114.4 (sh), 1019.6.

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {\includegraphics[width=0.5\textwidth]{2.1f}};
\end{tikzpicture}
\end{center}

**Ethyl 4,4-dimethylpent-2-ynoate (2.1f)\textsuperscript{47}:** Product isolated as a colorless oil (119.7 mg, 0.776 mmol, 74\%). \textsuperscript{1}H-NMR (400MHz, CDCl\textsubscript{3}) \(\delta 4.24-4.18 (q, J = 8 Hz, 2H), 1.32-1.28 (t, J = 8 Hz, 3H), 1.28 (s, 9H). \) IR (cm\textsuperscript{-1}): 2973.1, 2930.1 (sh), 2871.4, 2222.1, 1709.6 (vs), 1459.9 (w), 1365.8, 1272.1 (s), 1220.2 (vs), 1095.1 (vw), 1034.5 (s).

**General Procedure 2: Preparation of Ynoate Substrates (2.1b-2.1e):**

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {\includegraphics[width=0.5\textwidth]{2.1b}};
\end{tikzpicture}
\end{center}

Procedure adapted from the literature.\textsuperscript{48} Added to a flame-dried Schlenk flask, a solution of the corresponding 2,2-dibromoethenyl compound (1.0 equiv.) and dry THF (0.25 M) was cooled to 0°C under nitrogen. \textit{n}-BuLi (2.0 equiv.) was added dropwise, and
the reaction solution was stirred for 1 hr at this temperature. Ethyl chloroformate (1.5 equiv.) was added dropwise, and the reaction was allowed to warm to rt. The reaction solution was quenched with DI water after 1 hr, extracted with EtOAc, washed with brine, and dried over MgSO$_4$ to afford the crude product. The solvents were removed under reduced pressure, and the crude product was purified via column chromatography on silica gel with hexanes/EtOAc and concentrated to afford the ynoate compound.

Ynoate substrates 1b-1e are compounds known to literature.$^{48-50}$

![Structure 2.1b](image)

**Ethyl 3-(4-methoxyphenyl)-prop-2-ynoate (2.1b)$^{48}$:** Product isolated as a yellow-white solid (116.2 mg, 0.569 mmol, 68%). $^1$H-NMR (400MHz, CDCl$_3$) δ 7.55-7.53 (d, $J$ = 8 Hz, 2H), 6.89-6.87 (d, $J$ = 8 Hz, 2H), 4.31-4.26 (q, $J$ = 8 Hz, 2H), 3.83 (s, 3H), 1.37-1.33 (t, $J$ = 8 Hz, 3H). IR (cm$^{-1}$): 2986.5 (vw), 2934.3 (sh), 2203.1, 1700.3 (s), 1603.0, 1598.0, 1497.2 (w), 1444.8 (sh), 1370.2 (w), 1284.0 (s), 1250.2 (s), 1191.5 (s), 1158.2 (vs), 1022.0 (s).

![Structure 2.1c](image)

**Ethyl 3-(4-chlorophenyl)-prop-2-ynoate (2.1c)$^{48}$:** Product isolated as a red solid (520.0 mg, 2.887 mmol, 88%). $^1$H-NMR (400MHz, CDCl$_3$) δ 7.53-7.51 (d, $J$ = 8 Hz, 2H), 7.37-7.35 (d, $J$ = 8 Hz, 2H), 4.33-4.27 (q, $J$ = 8 Hz, 2H), 1.37-1.34 (t, $J$ = 8 Hz, 3H). IR (cm$^{-1}$):
2243.7 (sh), 2210.4, 1698.8 (s), 1592.8 (w), 1481.7, 1286.2 (vs), 1187.6 (vs), 1085.6, 1011.9.

(4-nitrophenyl)-Propynoic acid ethyl ester (2.1d): Product isolated as an orange solid (20.8 mg, 0.0949 mmol, 19%). $^1$H-NMR (400MHz, CDCl$_3$) δ 8.26-8.24 (d, $J = 8$ Hz, 2H), 7.76-7.74 (d, $J = 8$ Hz, 2H), 4.36-4.30 (q, $J = 8$ Hz, 2H), 1.39-1.36 (t, $J = 8$ Hz, 3H). IR (cm$^{-1}$): 2965.7 (sh), 2924.5, 2236.2 (w), 1701.1 (vs), 1600.3 (w), 1516.2 (vs), 1345.8 (s), 1290.1 (s), 1192.3 (vs), 1110.2 (sh), 1019.9.

O-Tolyl-propynoic acid ethyl ester (2.1e): Product isolated as an amber oil (235.0 mg, 1.249 mmol, 83%). $^1$H-NMR (400MHz, CDCl$_3$) δ 7.55-7.53 (d, $J = 8$ Hz, 1H), 7.35-7.31 (t, $J = 8$ Hz, 1H), 7.27-7.23 (t, $J = 8$ Hz, 1H), 7.16-7.20 (t, $J = 8$ Hz, 1H), 4.33-4.28 (q, $J = 8$ Hz, 2H), 2.49 (s, 3H), 1.38-1.34 (t, $J = 8$ Hz, 3H). IR (cm$^{-1}$): 2982.8 (vw), 2938.0 (sh), 2209.3 (sh), 2206.0, 1704.8 (vs), 1785.8 (w), 1366.7, 1294.0 (sh), 1185.7 (vs), 1023.4.
General Procedure 3: Preparation of Ynone Substrates (2.4a-2.4e):

![reaction diagram]

Procedure adapted from the literature.\textsuperscript{51} Added to a flame-dried Schlenk flask, a solution of phenylacetylene (1.0 equiv.) and dry THF (0.25 M) was cooled to 0°C under nitrogen. \textit{n}-BuLi (1.1 equiv.) was added dropwise, and the reaction solution was stirred for 1 hr at this temperature. The corresponding aldehyde (1.5 equiv.) was added dropwise, and the reaction was allowed to warm to rt. The reaction solution was quenched with DI water after 4 hr, extracted with EtOAc, and dried over MgSO\textsubscript{4}. The solvents were removed under reduced pressure to give the crude alcohol product to which DCM (0.25 M) and MnO\textsubscript{2} (10 equiv) were added and the solution was stirred at rt and in the dark for two hr. The reaction solution was filtered over celite, solvents were removed, and the crude product was purified via column chromatography on silica gel with hexanes/EtOAc and concentrated to afford the ynone compound.

The ynone substrates 2.4a-2.4e are compounds known to literature.\textsuperscript{51-54}

1,3-Diphenylprop-2-yn-1-one (2.4a): Product isolated as a white solid (220.2 mg, 1.068 mmol, 86%). \textsuperscript{1}H-NMR (400MHz, CDCl\textsubscript{3}) δ 8.25-8.22 (m, 2H), 7.71-7.69 (m, 2H), 7.66-7.62 (t, \textit{J} = 8 Hz, 1H), 7.55-7.52 (m, 2H), 7.51-7.48 (t, \textit{J} = 8 Hz, 1H), 7.45-7.41 (t, \textit{J} = 8
Hz, 2H). IR (cm\(^{-1}\)): 2195.6 (s), 1630.4 (vs), 1488.0, 1450.7, 1313.6, 1286.9 (s), 1206.5 (s), 1168.9, 1010.4 (s).

1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-one (2.4b)\(^{52}\): Product isolated as a yellow-white solid (519.3 mg, 2.198 mmol, 88%). \(^1\)H-NMR (400MHz, CDCl\(_3\)) \(\delta\) 8.22-8.18 (m, 2H), 7.69-7.67 (m, 2H), 7.50-7.46 (m, 1H), 7.44-7.40 (m, 2H), 7.01-6.98 (m, 2H), 3.91 (s, 3H). IR (cm\(^{-1}\)): 2194.9 (s), 1626.8 (s), 1594.9 (vs), 1569.8 (sh), 1510.5, 1420.7 (w), 1256.6 (s), 1155.2, 1027.9, 1009.2 (sh).

1-(4-bromophenyl)-3-phenylprop-2-yn-1-one (2.4c)\(^{53}\): Product isolated as a white solid (125.8 mg, 0.441 mmol, 88%). \(^1\)H-NMR (400MHz, CDCl\(_3\)) \(\delta\) 8.10-8.07 (m, 2H), 7.70-7.65 (m, 4H), 7.53-7.49 (m, 1H), 7.46-7.42 (t, \(J = 8\) Hz, 2H). IR (cm\(^{-1}\)): 2197.7 (vs), 1652.1, 1585.6 (w), 1394.5 (vw), 1298.5, 1206.7, 1169.7, 1067.7 (w).

4-Phenyl-3-butyne-2-one (2.4d)\(^{54}\): Product isolated as a clear, yellow oil (608.4 mg, 4.22 mmol, 86%). \(^1\)H-NMR (400MHz, CDCl\(_3\)) \(\delta\) 7.58-7.57 (d, \(J = 4\) Hz, 2H), 7.47-7.43 (m,
1-Cyclohexyl-3-phenylprop-2-yn-1-one (2.4e): Product isolated as a colorless oil (571.0 mg, 2.690 mmol, 94%). $^1$H-NMR (400MHz, CDCl$_3$) $\delta$ 7.59-7.57 (m, 2H), 7.47-7.43 (m, 1H), 7.40-7.36 (m, 2H), 2.09-2.03 (m, 2H), 1.84-1.79 (m, 2H), 1.55-1.45 (m, 2H), 1.39-1.32 (m, 2H), 1.30-1.21 (m, 2H). IR (cm$^{-1}$): 2929.0, 2854.1 (sh), 2197.7 (s), 1661.2 (vs), 1491.8 (w), 1446.4, 1262.5, 1142.0 (w), 1091.1 (sh), 1070.2.

Preparation of 1-Morpholino-3-phenylprop-2-yn-1-one (2.4f):

Procedure adapted from the literature.$^{55}$ To a flame-dried Schlenk flask containing a solution of 3-phenylpropionic acid (1.0 equiv.) and DCM (0.27 M), TEA (2.0 equiv.) and oxalyl chloride (1.3 equiv.) was added dropwise at 0°C under nitrogen. Morpholine (1.1 equiv.) was added, and the reaction proceeded at rt for 5 hr. The reaction solution was extracted with EtOAc, washed with brine and dried over Na$_2$SO$_4$ to afford the crude product. The solvents were removed under reduced pressure, and the crude product was purified via column chromatography on silica gel with hexanes/EtOAc and concentrated to afford 2.4f (247.1 mg, 1.148 mmol, 84%) as a yellow solid. $^1$H-NMR (400MHz, CDCl$_3$) $\delta$ 7.56-7.54 (d, $J = 8$ Hz, 2H), 7.45-7.42 (m, 1H), 7.39-7.35 (t, $J = 8$ Hz, 2H), 3.90 (s, 2H),
3.78-3.72 (m, 6H). IR (cm\(^{-1}\)) : 2920.8 (sh), 2864.7 (w), 2217.5, 1617.4 (vs), 1495.5, 1428.3 (s), 1278.8, 1213.1, 1110.0 (s), 1042.9.

**Preparation of 3-Phenylpropiolaldehyde (2.4g):**

\[
\text{Ph} \quad 1.) \quad \text{n-BuLi, THF, 0°C} \\
\text{Ph} \quad 2.) \quad \text{DMF} \quad \rightarrow \quad \text{Ph} \quad 2.4g
\]

Procedure adapted from the literature.\(^{56}\) To a flame-dried Schlenk flask, a solution of phenylacetylene (1.0 equiv.) and dry THF (0.25 M) was cooled to 0°C under nitrogen. n-BuLi (1.1 equiv.) was added dropwise, and the reaction solution was stirred for 1 hr. DMF (2 equiv.) was added followed by a temperature elevation to rt, and the solution stirred for 1 hr. The reaction solution was quenched with DI water, extracted with EtOAc, and dried over MgSO\(_4\). The solvents were removed under reduced pressure, and the crude product was purified via column chromatography on silica gel with hexanes/EtOAc and concentrated to afford 2.4g (94.4 mg, 0.7253 mmol, 36%) as a yellow oil. \(^1\)H-NMR (400MHz, CDCl\(_3\)) \(\delta\) 9.43 (s, 1H), 7.62-7.60 (m, 2H), 7.52-7.48 (m, 1H), 7.43-7.39 (m, 2H). IR (cm\(^{-1}\)) : 2953.6 (sh), 2924.0 (vs), 2853.9 (s), 1730.6 (w), 1461.8, 756.9 (w), 693.5 (w).

**Synthesis of (E)-Alkene Products (2.2a-2.2e, 2.5a-2.5g):**

\[
\text{Ph} \quad \text{O} \quad \text{OEt} \quad 1.5 \text{ equiv. PPh}_3 \quad 1.5 \text{ equiv. PhCO}_2\text{H} \\
25 \text{ equiv. H}_2\text{O} \\
\text{THF, 24 h, 65°C} \quad \rightarrow \quad \text{Ph} \quad \text{O} \quad \text{OEt} \quad 2.2a
\]

To an oven-dried 8 mL reaction vial was added PPh\(_3\) (1.5 equiv.), benzoic acid (1.5 equiv.), the corresponding substrate (1.0 equiv, 0.10 mmol), DI water (25 equiv.), and dry THF (0.1 M). The solution was heated to 65°C and stirred for 24 hr. The solvents were
removed under reduced pressure, toluene was added, and the solution dried over MgSO₄. The toluene was removed under reduced pressure, and cold Et₂O was added and filtered over silica. Et₂O was removed under reduced pressure, and the crude residue was purified via column chromatography on silica gel with hexanes/Et₂O (100:1 to 20:1) to afford the alkene product.

All (E)-alkene products 2.2a-2.2e and 2.5a-2.5g are compounds known to literature.⁵⁷-⁶⁶

The E/Z selectivity was 86:14 from ¹H-NMR spectroscopic analysis of the crude residue.

**trans-Ethyl cinnamate (2.2a)⁵⁷:** Product isolated as a colorless oil (14.2 mg, 0.0806 mmol, 81%). ¹H-NMR (400MHz, CDCl₃) δ 7.71-7.67 (d, J = 16 Hz, 1H), 7.54-7.52 (m, 2H), 7.39-7.38 (m, 3H), 6.46-6.42 (d, J = 16 Hz, 1H), 4.30-4.24 (q, J = 8 Hz, 2H), 1.36-1.33 (t, J = 8 Hz, 3H). ¹³C-NMR (101MHz, CDCl₃) δ 167.2, 144.7, 134.6, 130.4, 129.0, 128.2, 118.4, 60.7, 14.5. IR (cm⁻¹): 2925.0, 2861.0 (sh), 1712.4 (vs), 1638.3, 1450.1 (w), 1368.4 (w), 1309.7, 1268.2 (w), 1201.4 (sh), 1171.4 (vs), 1039.2, 980.0.

**cis-Ethyl cinnamate (2.3a):** Product isolated as a colorless oil (1.8 mg, 0.0102 mmol, 10%). Total yield (16.0 mg, 0.0908 mmol, 91%).

The E/Z selectivity was 92:8 from ¹H-NMR spectroscopic analysis of the crude residue.
Ethyl \((E)\)-3-(4-methoxyphenyl) acrylate \((2.2b)\)^58: Product isolated as a white solid (16.7 mg, 0.0810 mmol, 84%). \(^1\)H-NMR (400MHz, CDCl\(_3\)) δ 7.66-7.62 (d, \(J = 16\) Hz, 1H), 7.49-7.47 (d, \(J = 8\) Hz, 2H), 6.91-6.89 (d, \(J = 8\) Hz, 2H), 6.33-6.29 (d, \(J = 16\) Hz, 1H), 4.28-4.23 (q, \(J = 8\) Hz, 2H), 3.84 (s, 3H), 1.35-1.31 (t, \(J = 8\) Hz, 3H). \(^13\)C-NMR (101MHz, CDCl\(_3\)) δ 167.5, 161.5, 144.4, 129.8, 127.3, 115.9, 114.4, 60.5, 55.5, 14.5. IR (cm\(^{-1}\)): 1706.8, 1633.7 (w), 1604.0, 1512.2, 1304.3 (sh), 1288.5 (w), 1252.1 (s), 1167.4 (vs), 1031.6. MP: 45.2-46.6°C.

![Structure of 2.2c](image)

The \(E/Z\) selectivity was 75:25 from \(^1\)H-NMR spectroscopic analysis of the crude residue.

Ethyl \((E)\)-3-(4-chlorophenyl) acrylate \((2.2c)\)^59: Product isolated as a colorless oil (15.7 mg, 0.0745 mmol, 68%). \(^1\)H-NMR (400MHz, CDCl\(_3\)) δ 7.65-7.61 (d, \(J = 16\) Hz, 1H), 7.46-7.43 (m, 2H), 7.37-7.34 (m, 2H), 6.42-6.38 (d, \(J = 16\) Hz, 1H), 4.29-4.24 (q, \(J = 8\) Hz, 2H), 1.35-1.31 (t, \(J = 8\) Hz, 3H). \(^13\)C-NMR (101MHz, CDCl\(_3\)) δ 166.8, 143.2, 136.2, 133.0, 129.3, 129.2, 118.9, 60.7, 14.4. IR (cm\(^{-1}\)): 1710.4 (s), 1638.2, 1491.1, 1309.1 (s), 1268.5, 1201.1 (sh), 1168.1 (vs), 1088.2, 1035.6, 980.4.

Ethyl \((Z)\)-3-(4-chlorophenyl) acrylate \((2.3c)\): Product isolated as a colorless oil (3.4 mg, 0.0161 mmol, 15%). Total yield (19.1 mg, 0.0907 mmol, 83%).
The E/Z selectivity was 76:24 from $^1$H-NMR spectroscopic analysis of the crude residue. Isomers of the product were inseparable through column chromatography. Total yield (17.4 mg, 0.0787 mmol, 90%).

**Ethyl (E)-3-(4-nitrophenyl) acrylate (2.2d)**: Product isolated as a tan solid. $^1$H-NMR (400MHz, CDCl$_3$) δ 8.26-8.24 (d, $J = 8$ Hz, 2H), 7.73-7.66 (m, 3H), 6.58-6.54 (d, $J = 16$ Hz, 1H), 4.32-4.27 (q, $J = 8$ Hz, 2H), 1.37-1.33 (t, $J = 8$ Hz, 3H). $^{13}$C-NMR (101MHz, CDCl$_3$) δ 166.1, 148.5, 141.7, 140.7, 128.7, 124.3, 122.7, 61.1, 14.4. IR (cm$^{-1}$): 1710.2 (vs), 1645.2 (w), 1596.7 (w), 1518.0, 1343.9 (vs), 1310.4 (sh), 1192.4, 1117.3 (w), 1031.8 (w), 978.7 (w). MP: 130.6-133.3°C.

![2.2e](image)

The E/Z selectivity was 42:58 from $^1$H-NMR spectroscopic analysis of the crude residue. Isomers of the product were inseparable through column chromatography. Total yield (18.0 mg, 0.0946 mmol, 68%).

**Ethyl (E)-3-(o-tolyl) acrylate (2.2e)**: Product isolated as a yellow oil. $^1$H-NMR (400MHz, CDCl$_3$) δ $^{13}$C-NMR (101MHz, CDCl$_3$) δ 168.6, 142.4, 130.9, 130.1, 126.5, 126.4, 119.4, 60.7, 19.9, 14.5. IR (cm$^{-1}$): 2924.3 (vs), 2859.6, 1717.3 (s), 1639.0 (w), 1467.2 (w), 1318.0, 1269.4, 1179.8 (s), 1041.7 (w), 985.7 (vw).
The E/Z selectivity of the reaction was >99:1 from 1H-NMR spectroscopic analysis of the crude residue.

(E)-Chalcone (2.5a): Product isolated as a white solid (17.1 mg, 0.0821 mmol, 90%).

1H-NMR (400MHz, CDCl3) δ 7.71-7.67 (d, J = 16 Hz, 1H), 7.54-7.52 (m, 2H), 7.39-7.38 (m, 3H), 6.46-6.42 (d, J = 16 Hz, 1H), 4.30-4.24 (q, J = 8 Hz, 2H), 1.36-1.33 (t, J = 8 Hz, 3H). 13C-NMR (101MHz, CDCl3) δ 167.2, 144.7, 134.6, 130.4, 129.0, 128.2, 118.4, 60.7, 14.5. IR (cm⁻¹): 2925.0, 2861.0 (sh), 1712.4 (vs), 1638.3, 1450.1 (w), 1368.4 (w), 1309.7, 1268.2 (w), 1201.4 (sh), 1171.4 (vs), 1039.2, 980.0. MP: 51.6-54.4°C.

(E)-1-(4-methoxyphenyl)-3-phenylprop-2-en-1-one (2.5b): Product isolated as a white solid (15.6 mg, 0.0655 mmol, 68%).

1H-NMR (400MHz, CDCl3) δ 8.06-8.04 (d, J = 8 Hz, 2H), 7.83-7.79 (d, J = 16 Hz, 1H), 7.65-7.64 (m, 2H), 7.57-7.53 (d, J = 16 Hz, 1H), 7.43-7.41 (m, 3H), 7.00-6.98 (d, J = 8 Hz, 2H), 3.90 (s, 3H). 13C-NMR (101MHz, CDCl3) δ 188.9, 163.6, 144.1, 135.2, 131.2, 131.0, 130.5, 129.1, 128.5, 122.0, 114.0, 55.7. IR (cm⁻¹): 2917.0 (w), 1656.4, 1597.6 (vs), 1570.8 (sh), 1255.6, 1220.6, 1181.0 (s), 1013.9, 971.7 (s). MP: 98.9-100.6°C.
The E/Z selectivity of the reaction was >99:1 from $^1$H-NMR spectroscopic analysis of the crude residue.

(E)-1-(4-bromophenyl)-3-phenylprop-2-en-1-one (2.5c)\textsuperscript{63}: Product isolated as a white solid (27.3 mg, 0.0951 mmol, 83%). $^1$H-NMR (400MHz, CDCl\textsubscript{3}) $\delta$ 7.90-7.88 (d, $J$ = 8 Hz, 2H), 7.84-7.80 (d, $J$ = 16 Hz, 1H), 7.66-7.64 (m, 4H), 7.50-7.46 (d, $J$ = 16 Hz, 1H), 7.44-7.42 (m, 3H). $^{13}$C-NMR (101MHz, CDCl\textsubscript{3}) $\delta$ 189.6, 145.6, 137.1, 134.8, 132.1, 130.9, 130.2, 129.2, 128.7, 128.1, 121.6. IR (cm\textsuperscript{-1}): 2924.8, 1659.1 (vs), 1603.4 (vs), 1583.1 (sh), 1450.7 (w), 1336.1, 1217.8, 1069.4, 1008.5, 982.2. MP: 97.2-98.9°C

(E)-4-phenylbut-3-en-one (2.5d)\textsuperscript{64}: Product isolated as a yellow oil (9.8 mg, 0.0670 mmol, 71%). $^1$H-NMR (400MHz, CDCl\textsubscript{3}) $\delta$ 7.56-7.50 (m, 3H), 7.41-7.40 (m, 3H), 6.74-6.70 (d, $J$ = 16 Hz, 1H), 2.39 (s, 3H). $^{13}$C-NMR (101MHz, CDCl\textsubscript{3}) $\delta$ 198.6, 143.6, 130.7, 129.1, 128.4, 127.3, 27.7. IR (cm\textsuperscript{-1}): 2855.0 (vw), 2810.0 (sh), 1690.2 (sh), 1668.1 (vs), 1601.0, 1450.5 (w), 1358.8 (w), 1256.8 (s), 1204.5 (w), 1178.4 (w).
The \( E/Z \) selectivity was 98:2 from \(^1\)H-NMR spectroscopic analysis of the crude residue.

\((E)\)-1-cyclohexyl-3-phenylprop-2-en-1-one (2.5e): Product isolated as a white solid (18.1 mg, 0.845 mmol, 91%).  \(^1\)H-NMR (400MHz, CDCl\(_3\)) \( \delta \) 7.61-7.55 (m, 3H), 7.40-7.38 (m, 3H), 6.84-6.80 (d, \( J = 16 \) Hz, 1H), 2.70-2.63 (m, 1H), 1.92-1.88 (m, 2H), 1.86-1.81 (m, 2H), 1.73-1.69 (m, 1H), 1.48-1.23 (m, 5H).  \(^{13}\)C-NMR (101MHz, CDCl\(_3\)) \( \delta \) 203.4, 142.4, 134.9, 130.4, 129.0, 128.4, 124.9, 49.6, 28.9, 26.1, 25.9.  IR (cm\(^{-1}\)): 2928.7 (s), 1680.4 (s), 1604.8 (s), 1464.6, 1338.4, 1319.7, 1200.0, 1065.8.  MP: 54.8-56.2°C.

The \( E/Z \) selectivity was 95:5 from \(^1\)H-NMR spectroscopic analysis of the crude residue.

\((E)\)-1-morpholino-3-phenylprop-2-en-1-one (2.5f): Product isolated as a white solid (10.0 mg, 0.0460 mmol, 53%).  \(^1\)H-NMR (400MHz, CDCl\(_3\)) \( \delta \) 7.72-7.68 (d, \( J = 16 \) Hz, 1H), 7.54-7.51 (m, 2H), 7.38-7.36 (m, 3H), 6.86-6.82 (d, \( J = 16 \) Hz, 1H), 3.73 (s, 8H).  \(^{13}\)C-NMR (101MHz, CDCl\(_3\)) \( \delta \) 165.7, 143.4, 135.2, 129.9, 128.9, 127.9, 116.6, 67.0.  IR (cm\(^{-1}\)): 2923.8, 2853.8, 1649.1 (vs), 1603.7, 1459.2 (sh), 1431.4, 1228.3, 1115.2, 1044.0 (w), 977.9 (w).  MP: 60.1-63.5°C.
The E/Z selectivity was 76:24 from $^1$H-NMR spectroscopic analysis of the crude residue.

**trans-Cinnamaldehyde (2.5g)**: Product isolated as a yellow oil (9.6 mg, 0.0726 mmol, 77%). $^1$H-NMR (400MHz, CDCl$_3$) $\delta$ 9.73-9.71 (d, $J$ = 8 Hz, 1H), 7.59-7.57 (m, 2H), 7.51-7.47 (d, $J$ = 16 Hz, 1H), 7.47-7.44 (m, 3H), 6.76-6.70 (dd, $J$ = 8 Hz, 16Hz, 1H). $^{13}$C-NMR (101MHz, CDCl$_3$) $\delta$ 193.9, 152.9, 134.1, 131.4, 129.2, 128.7, 128.6. IR (cm$^{-1}$): 2924.8 (w), 2853.3 (w), 1676.7 (vs), 1625.8, 1450.4 (vw), 1254.3 (vw), 1123.5, 973.0.

**Synthesis of (Z)-Alkene Products (2.3a-2.3e):**

$$\text{Ph} = \text{Et}$$

To an oven-dried 8 mL reaction vial was added PPh$_3$ (1.5 equiv.), the corresponding substrate (1.0 equiv, 0.10 mmol), DI water (40 equiv.), and dry THF (0.1 M). The solution was heated to 65°C and stirred for 24 hr. The solvents were removed under reduced pressure, toluene was added, and the solution dried over MgSO$_4$. The toluene was removed under reduced pressure, and cold Et$_2$O was added and filtered over silica. Et$_2$O was removed under reduced pressure, and the crude residue was purified via column chromatography on silica gel with hexanes/Et$_2$O (100:1 to 10:1) to afford the alkene product.

All cis-alkene products 2.3a-2.3e are compounds known to literature. $^{67-70}$
The E/Z selectivity was 15:85 from $^1$H-NMR spectroscopic analysis of the crude residue.

**cis-Ethyl cinnamate (2.3a)**: Product isolated as a colorless oil (10.1 mg, 0.0573 mmol, 56%). $^1$H-NMR (400MHz, CDCl$_3$) δ 7.59-7.57 (m, 2H), 7.37-7.32 (m, 3H), 6.97-6.94 (d, $J = 12$ Hz, 1H), 5.97-5.94 (d, $J = 12$ Hz, 1H), 4.20-4.15 (q, $J = 8$ Hz, 2H), 1.26-1.23 (t, $J = 8$ Hz, 3H). $^{13}$C-NMR (101MHz, CDCl$_3$) δ 166.3, 143.1, 135.0, 129.8, 129.1, 128.1, 120.0, 60.4, 14.2. IR (cm$^{-1}$): 2924.1, 2853.7 (sh), 1720.1 (s), 1629.5, 1452.2 (w), 1262.3 (w), 1161.6 (vs), 1028.5, 830.3 (w).

**trans-Ethyl cinnamate (2.2a)**: Product isolated as a colorless oil (2.1 mg, 0.0119 mmol, 12%). Total yield (12.2 mg, 0.0692 mmol, 68%).

The E/Z selectivity was 22:78 from $^1$H-NMR spectroscopic analysis of the crude residue.

**Ethyl (Z)-3-(4-methoxyphenyl) acrylate (2.3b)**: The (Z)-isomer was inseparable from the remaining starting material through column chromatography. $^1$H-NMR (400MHz, CDCl$_3$) δ 7.70-7.68 (d, $J = 8$ Hz, 2H), 6.87-6.83 (m, 3H), 5.84-5.81 (d, $J = 12$ Hz, 1H), 4.22-4.16 (q, $J = 8$ Hz, 2H), 3.83 (s, 3H), 1.30-1.26 (t, $J = 8$ Hz, 3H).
The $E$/Z selectivity was 12:88 from $^1$H-NMR spectroscopic analysis of the crude residue.

**Ethyl ($Z$)-3-(4-chlorophenyl) acrylate (2.3c):** Product isolated as a colorless oil (21.6 mg, 0.1026 mmol, 68%). $^1$H-NMR (400MHz, CDCl$_3$) $\delta$ 7.56-7.54 (d, $J = 8$ Hz, 2H), 7.33-7.31 (d, $J = 8$ Hz, 2H), 6.90-6.87 (d, $J = 12$ Hz, 1H), 5.97-5.94 (d, $J = 12$ Hz, 1H), 4.20-4.15 (q, $J = 8$Hz, 2H), 1.28-1.24 (t, $J = 8$ Hz, 3H). $^{13}$C-NMR (101MHz, CDCl$_3$) $\delta$ 166.0, 142.0, 135.0, 133.3, 131.3, 128.3, 120.5, 60.5, 14.2. IR (cm$^{-1}$): 1718.0 (s), 1630.8, 1591.5 (vw), 1491.2, 1442.1 (vw), 1397.9 (w), 1175.2 (vs), 1092.8, 1029.4, 1016.1, 849.1.

**Ethyl ($E$)-3-(4-chlorophenyl) acrylate (2.2c):** Product isolated as a colorless oil (3.6 mg, 0.0171 mmol, 10%). Total yield (25.2 mg, 0.1196 mmol, 80%).

The $E$/Z selectivity was 28:72 from $^1$H-NMR spectroscopic analysis of the crude residue.

Isomers of the product were inseparable through column chromatography. Total yield (9.8 mg, 0.0443 mmol, 87%).

**Ethyl ($Z$)-3-(4-nitrophenyl) acrylate (2.3d):** Product isolated as yellow solid. $^1$H-NMR (400MHz, CDCl$_3$) $\delta$ 8.22-8.20 (d, $J = 8$ Hz, 2H), 7.68-7.66 (d, $J = 8$ Hz, 2H), 7.03-6.99 (d,
$J = 12 \text{ Hz}, 1\text{H}), 6.14-6.11 \text{ (d, } J = 12 \text{ Hz, } 1\text{H}), 4.20-4.15 \text{ (q, } J = 8 \text{ Hz, } 2\text{H}), 1.26-1.22 \text{ (t, } J = 8 \text{ Hz, } 3\text{H})$. $^{13}\text{C-NMR (101MHz, CDCl}_3\text{) } \delta 165.4, 147.6, 141.6, 140.7, 130.3, 123.4, 123.3, 60.8, 14.1$. IR (cm$^{-1}$): 2930.3, 1718.1 (vs), 1596.9, 1521.1 (vs), 1466.7 (vw), 1345.2 (s), 1299.4 (w), 1218.1 (s), 1058.3 (w), 857.3 (w). MP: 85.6-87.9°C.

The $E/Z$ selectivity was 2:98 from $^1\text{H-NMR}$ spectroscopic analysis of the crude residue.

**Ethyl (Z)-3-(o-tolyl) acrylate (2.3e)**: Product isolated as a tan oil (15.4 mg, 0.0809 mmol, 69%). $^1\text{H-NMR (400MHz, CDCl}_3\text{) } \delta 7.22-7.15 \text{ (m, } 4\text{H}), 7.14-7.11 \text{ (d, } J = 12 \text{ Hz, } 1\text{H}), 6.04-6.01 \text{ (d, } J = 12 \text{ Hz, } 1\text{H}), 4.11-4.06 \text{ (q, } J = 8 \text{ Hz, } 2\text{H}), 1.11-1.08 \text{ (t, } J = 8 \text{ Hz, } 3\text{H})$. $^{13}\text{C-NMR (101MHz, CDCl}_3\text{) } \delta 159.2, 143.1, 129.7, 128.9, 128.5, 125.3, 121.2, 60.3, 20.0, 14.1$. IR (cm$^{-1}$): 2962.0 (sh), 2924.0 (vs), 2851.6, 1735.5, 1465.1, 1381.3 (w), 1267.0 (w), 1175.6, 1118.5 (w), 1023.3 (w), 977.6.
3. Phosphine-Mediated Partial Reduction of Ynones to Selectively Achieve (Z)-Enones

3.1 Project Scope

The selective reduction of alkynes to alkenes is still a challenging problem in organic synthesis. Even established methods using Lindlar’s catalyst or dissolving metal conditions are not always applicable with alkynes that exhibit complex functional groups. This is due to the competitive reducible nature of these other functional groups compared with the alkyne. Additionally, the reagents used in these quasi-selective methods are often harsh, while newer, milder methodologies generally require the use of a transition metal-catalyst. Furthermore, in order to obtain selectivity between the (E)- or (Z)-isomer of the resulting alkene, different reaction conditions must be used for each scenario. Due to the potential for over reduction, alkynyl carbonyls such as ynones and ynoates specifically experience limited reduction methodologies. The typical methods to selectively form (E)-enones involve hydride reagents or even enzyme catalysis. In the case of selectively forming (Z)-enones, methods generally rely on palladium catalysts and \( \text{H}_2 \). The resulting enones are important due to their ability to be used as synthetic building blocks, as well as their presence in various natural products.

Phosphine-mediated partial reduction of alkynes to form the corresponding alkenes has been reported, most recently by our group. Early reports of this chemistry illustrated the capabilities of this phosphine-mediated partial reduction, but the selectivity
between the \((E)\)- and \((Z)\)-alkenes formed were not well controlled, or only produced the \((E)\)-isomer, and the reaction scope was not well established. Through our previous work, a method was established in which this phosphine-mediated partial reduction could be accomplished with high stereoselectivity and yield, for a much broader reaction scope.\(^{76}\)

Experimental evidence suggests that the alkyne reduction primarily produces the corresponding \((Z)\)-alkene and triphenylphosphine oxide (see Chapter 2 for mechanism). After \((Z)\)-alkene formation, a \((Z)\)- to \((E)\)-isomerization occurs, catalyzed by excess phosphine, in which the phosphine adds to the \((Z)\)-alkene to form a zwitterionic intermediate capable of undergoing free rotation (Scheme 3.1). This results in the formation of the thermodynamically favored \((E)\)-alkene after the elimination of the phosphine.

**Scheme 3.1: Proposed \((Z)\)- to \((E)\)-Alkene Isomerization**

Despite the significant advances in phosphine-mediated partial reduction from our research, the selective formation of \((Z)\)-enones from alkylnyl ketones was unable to be accomplished due to their higher reactivity compared to alkylnyl esters. Due to the relative electronic and steric properties of the alkyne and corresponding alkene, the \((Z)\)- to \((E)\)-alkene isomerization is inherently energetically less favorable than the alkyne reduction. Sterically, the decreased bond angle of the alkene, compared to the alkyne, hinders the phosphine nucleophilic addition. Similarly, the lower electrophilicity of the alkene,
compared to the alkyne, also inhibits phosphine nucleophilic addition. As such, a bulkier phosphine diminishes the performance of the alkene isomerization, previously described (Scheme 3.2). Therefore, it is hypothesized that in order to achieve this stereoselective phosphine-mediated partial reduction of the more reactive ynones, much more consideration must be given to the nature of the phosphine and the reaction conditions used. Additionally, examination of phosphine effects may also give further insight into the mechanism of these reactions.

Scheme 3.2: Stereoselective Effects of Bulkier Phosphine

Regarding the nature of the phosphine, two tunable qualities may be manipulated to achieve the (Z)-isomer stereoselectively; namely, the relative steric hindrance and nucleophilicity of the phosphine. Firstly, a phosphine more sterically hindered than PPh$_3$ may be capable of carrying out the partial reduction of an ynone, but too sterically restricted to re-attack and isomerize the corresponding (Z)-enone. This hypothesis is founded on the molecular geometry of the alkyne, with a bond angle of 180°, compared with an alkene, with a bond angle approximately 120°. Evaluating this property based on the phosphine’s cone angle shows that many phosphines possess the inherent quality of being more sterically restricted than PPh$_3$ (Figure 3.1). It is worth noting that the ideal phosphine must not be too sterically hindered to prohibit the reaction from occurring at all. Moreover, temperature and time are critical parameters for optimizing the phosphine’s utility; for
example, creating a scenario in which the partial reduction occurs rapidly while avoiding alkene isomerization would be ideal.

*Figure 3.1: Sterically Hindered Phosphines Based on Cone Angle*

<table>
<thead>
<tr>
<th>Cone Angle</th>
<th>PPh₃</th>
<th>CH₃</th>
<th>CH₃</th>
<th>PCy₂</th>
<th>CH₃</th>
<th>CH₃</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>145°</td>
<td>161°</td>
<td>170°</td>
<td>176°</td>
<td>184°</td>
<td>194°</td>
</tr>
</tbody>
</table>

Secondly, the electronics of the phosphine are equally as important to consider; a phosphine less nucleophilic than PPh₃ could theoretically prevent the isomerization reaction from occurring due to alkynes being more electrophilic than alkenes. There are a variety of phosphines less nucleophilic than PPh₃ that may be capable of avoiding the alkene isomerization (Figure 3.2). Again, the ideal phosphine in this regard must not be such a poor nucleophile that it would prohibit the intended partial reduction from occurring.

*Figure 3.2: Electron-Poor Phosphines*

Finally, these tunable qualities need not be independent of each other; likely the ideal phosphine will result from both steric and electronic tuning. As such, only through a thorough examination of the phosphine scope can insight be gained for these complex phosphine-substrate interactions and influences. Once the ideal phosphine has been established, general reaction conditions may be expected to found as well.
3.2 Phosphine Scope

3.2.1 Phosphine Sterics

When initially considering the phosphine scope, a phosphine slightly more sterically hindered than PPh$_3$ was examined (Scheme 3.3). 1,3-Diphenylprop-2-yn-1-one was chosen as the initial substrate due to its neutral electronics at both terminal positions. Remarkably, PPh$_2$(o-tolyl) illustrated the capability to produce a majority of the (Z)-chalcone isomer, significantly altering the $>99:1$ (E)-/(Z)-ratio previously reported; albeit, in low stereoselectivity and yield.

Scheme 3.3: Comparison of PPh$_2$(o-tolyl) and PPh$_3$

<table>
<thead>
<tr>
<th>Compound</th>
<th>Reaction Conditions</th>
<th>E/Z Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPh$_2$(o-tolyl)</td>
<td>THF/H$_2$O, 65°C, 24 h</td>
<td>43:57 (38%)</td>
</tr>
<tr>
<td>PPh$_3$</td>
<td>THF, 24 h, 65°C</td>
<td>90% (&gt;99:1)</td>
</tr>
</tbody>
</table>

After PPh$_2$(o-tolyl) showed the capacity to provide the desired (Z)-enone, optimal reaction conditions were screened (Table 3.1). As expected, to avoid the alkene isomerization, the phosphine stoichiometry needed to be slightly less than one equivalent (entries 1-3). It was found that the optimal amount of water added was greater than in our previous study, and provided a moderate increase in yield and desired stereoselectivity (entries 4-6). To avoid nucleophilic addition by the solvent, non-protic solvents were examined, with THF and DCE producing similar results (entries 5 and 7). Overall, the efficiency of the reaction was found to be highly dependent on the concentration. In general, higher concentration resulted in increased yield and lower desired stereoselectivity (entries 9-12).
After reaction conditions were somewhat optimized, a short phosphine scope was developed (Table 3.2). These results showed PPh\textsubscript{2}(o-tolyl) to be the best phosphine for achieving the desired stereoselectivity due to: (1) steric constraints exhibited by other phosphines (entries 2-5); or (2) the increased nucleophilicity exhibited by PC\textsubscript{y}3. To determine the thermodynamic influences on yield and stereoselectivity, a temperature profile was established for o-tolyl phosphines (Table 3.3).

Table 3.1: Optimization of Reaction Conditions for PPh\textsubscript{2}(o-tolyl)

| Entry | Phos. Equiv. | Water Equiv | Solvent | Conc. | NMR Yield (E:Z)
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.0</td>
<td>40</td>
<td>THF</td>
<td>0.1 M</td>
<td>32% (45:55)</td>
</tr>
<tr>
<td>2</td>
<td>0.95</td>
<td>40</td>
<td>THF</td>
<td>0.1 M</td>
<td>28% (33:67)</td>
</tr>
<tr>
<td>3</td>
<td>0.80</td>
<td>40</td>
<td>THF</td>
<td>0.1 M</td>
<td>27% (32:68)</td>
</tr>
<tr>
<td>4</td>
<td>0.95</td>
<td>25</td>
<td>THF</td>
<td>0.1 M</td>
<td>10% (45:55)</td>
</tr>
<tr>
<td>5</td>
<td>0.95</td>
<td>55</td>
<td>THF</td>
<td>0.1 M</td>
<td>44% (39:61)</td>
</tr>
<tr>
<td>6</td>
<td>0.95</td>
<td>85</td>
<td>THF</td>
<td>0.1 M</td>
<td>56% (42:58)</td>
</tr>
<tr>
<td>7</td>
<td>0.95</td>
<td>55</td>
<td>DCE</td>
<td>0.1 M</td>
<td>47% (32:68)</td>
</tr>
<tr>
<td>8</td>
<td>0.95</td>
<td>55</td>
<td>Toluene</td>
<td>0.1 M</td>
<td>4% (&gt;1:99)</td>
</tr>
<tr>
<td>9</td>
<td>0.95</td>
<td>55</td>
<td>THF</td>
<td>0.05 M</td>
<td>7% (37:63)</td>
</tr>
<tr>
<td>10</td>
<td>0.95</td>
<td>55</td>
<td>THF</td>
<td>0.25 M</td>
<td>58% (46:54)</td>
</tr>
<tr>
<td>11</td>
<td>0.95</td>
<td>55</td>
<td>THF</td>
<td>0.50 M</td>
<td>74% (48:52)</td>
</tr>
<tr>
<td>12</td>
<td>0.95</td>
<td>55</td>
<td>THF</td>
<td>0.75 M</td>
<td>74% (68:32)</td>
</tr>
</tbody>
</table>

*The reactions were run with ynone 2.4a (0.15 mmol). Y and (E):Z ratio were determined via \textsuperscript{1}H NMR using TCE as the internal standard.

Table 3.2: Phosphine Scope for Selected Substrate

<table>
<thead>
<tr>
<th>Entry</th>
<th>PR\textsubscript{3}</th>
<th>NMR Yield (E:Z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PC\textsubscript{y}3</td>
<td>79% (97:3)</td>
</tr>
<tr>
<td>2</td>
<td>P(o-tolyl)\textsubscript{3}</td>
<td>NR</td>
</tr>
<tr>
<td>3</td>
<td>PPh(o-tolyl)\textsubscript{2}</td>
<td>NR</td>
</tr>
<tr>
<td>4</td>
<td>SPhos</td>
<td>NR</td>
</tr>
<tr>
<td>5</td>
<td>CyJohnPhos</td>
<td>2% (&lt;99:1)</td>
</tr>
</tbody>
</table>
Table 3.3: Temperature Profile for Selected Phosphines

<table>
<thead>
<tr>
<th>Entry</th>
<th>PR₃</th>
<th>Temperature (°C)</th>
<th>NMR Yield (E:Z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PPh₂(o-tolyll)</td>
<td>30</td>
<td>60% (89:11)</td>
</tr>
<tr>
<td>2</td>
<td>PPh₂(o-tolyll)</td>
<td>50</td>
<td>74% (66:34)</td>
</tr>
<tr>
<td>3</td>
<td>PPh₂(o-tolyll)</td>
<td>80</td>
<td>99% (50:50)</td>
</tr>
<tr>
<td>4</td>
<td>PPh₁(o-tolyll)₂</td>
<td>80</td>
<td>NR</td>
</tr>
<tr>
<td>5</td>
<td>PPh₂(o-tolyll)₃</td>
<td>80</td>
<td>NR</td>
</tr>
</tbody>
</table>

Dissatisfied by the results, a less conjugated substrate was evaluated in hopes of providing a more selective reaction by avoiding bias from the conjugated system. To our delight, the yield and (E)- to (Z)-ratio significantly improved, illustrating a distinguishable difference between alkyl and aryl ynones within this system (Scheme 3.4). The success with the cyclohexyl ynone substrate did not carry over to a methyl ynone. As such, reaction conditions were further optimized (Table 3.4).
Table 3.4: *Optimization of Conditions for Alkyl Ynones*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Conc.</th>
<th>Time (h)</th>
<th>NMR Yield (E:Z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65</td>
<td>0.5 M</td>
<td>20</td>
<td>92% (56:44)</td>
</tr>
<tr>
<td>2</td>
<td>65</td>
<td>0.075 M</td>
<td>48</td>
<td>50% (17:83)</td>
</tr>
<tr>
<td>3</td>
<td>65</td>
<td>0.15 M</td>
<td>24</td>
<td>80% (26:74)</td>
</tr>
<tr>
<td>4</td>
<td>65</td>
<td>0.25 M</td>
<td>24</td>
<td>99% (46:54)</td>
</tr>
<tr>
<td>5</td>
<td>65</td>
<td>0.15 M</td>
<td>0.5</td>
<td>6% (&gt;1:99)</td>
</tr>
<tr>
<td>6</td>
<td>65</td>
<td>0.15 M</td>
<td>1</td>
<td>10% (&gt;1:99)</td>
</tr>
<tr>
<td>7</td>
<td>65</td>
<td>0.15 M</td>
<td>2</td>
<td>27% (23:77)</td>
</tr>
<tr>
<td>8</td>
<td>65</td>
<td>0.15 M</td>
<td>4</td>
<td>61% (31:69)</td>
</tr>
<tr>
<td>9</td>
<td>65</td>
<td>0.15 M</td>
<td>8</td>
<td>78% (27:73)</td>
</tr>
<tr>
<td>10</td>
<td>80</td>
<td>0.15 M</td>
<td>8</td>
<td>88% (23:77)</td>
</tr>
<tr>
<td>11</td>
<td>80</td>
<td>0.15 M</td>
<td>20</td>
<td>98% (21:79)</td>
</tr>
</tbody>
</table>

*The reactions were run with ynone 2.4d (0.15 mmol). Yield and (E):(Z) ratio were determined via ¹H NMR using TCE as the internal standard.*

Many concentrations were examined over many time iterations; however, only relevant concentration dependent time studies are reported (entries 1-6). Overall, in order to achieve a reasonable reaction time for efficient stereoselective product formation, a concentration of 0.15 M was chosen. Based on these results, it was found that the (E)-(Z)-stereoselectivity decreased over some time, and then slightly increased over the course of the reaction. (entries 3, 5-9). This finding may suggest that at the time necessary to complete a small amount of product formation, enough phosphine is still present to competitively perform the alkene isomerization, despite theoretically being less energetically favorable than the phosphine-mediated reduction; however, kinetic studies would be necessary to confirm this. However, the reaction exhibited a sharp spike in product formation early on (2-4 h). Once this occurs, alkene isomerization is seemingly less influential towards the diastereomeric outcome, likely attributed to insufficient phosphine. As such, it is inferred that at some ratio of alkyne/(Z)-alkene/phosphine, the
reaction can proceed to almost exclusively produce the (Z)-enone. In order to reach the highest yield as fast as possible (in hopes to further disfavor alkene isomerization), the temperature was increased to 80°C, and monitored over time (entries 7-8). The temperature change proved fortuitous, as it resulted in a slight increase in stereoselectivity, as well as a moderate increase in yield.

Following this optimization, a small substrate scope was developed for several alkyl ynones (Scheme 3.5). The reaction conditions developed for the substrate scope afforded moderate to high yields, all with similar stereoselectivities. Despite the high reaction yields obtained from PPh₂(o-tolyl), stereoselectivity could still be improved. Two phosphines slightly more sterically hindered than PPh₂(o-tolyl), were explored. (Scheme 3.6). Unfortunately, phosphine 3.2b proved to be too sterically hindered and resulted in very poor yield. It was thought that phosphine 3.2c could potentially contribute only a slight degree of increased steric bias compared to PPh₂(o-tolyl); however, stereoselective control diminished with this phosphine due to the added nucleophilicity contributed by the additional electron donating alkyl group. Overall, stereoselective control of this phosphine-mediated reduction based on phosphine sterics reached a limit for what one would consider reasonable reaction conditions, and attention was turned instead towards electron deficient phosphines relative to PPh₃.
3.2.2 Phosphine Electronics

The first phosphine less nucleophilic than PPh$_3$ examined utilized the same conditions as those used for the sterically hindered phosphine system (Scheme 3.7).

Remarkably, a simple mono-fluorinated aryl substituent proved capable of predominantly achieving the desired (Z)-enone, illustrating the electronic and steric neutrality of PPh$_3$ when used in this system.$^{76}$ Although (p-fluoro)PPh$_2$ demonstrated the ability to provide the desired (Z)-enone in good yield, the stereoselectivity was still lacking, so reaction conditions were optimized for more electron-poor phosphines (Table 3.5).

Based on time studies performed at 80°C, the overall reduction reaction occurred much faster for the electron deficient phosphines than the sterically constrained phosphines. Additionally, it was observed from temperature independent time studies that alkene isomerization readily occurred at any temperature; however, it was noticed that the alkene isomerization needed more time to occur than the reduction. Therefore, both time
and temperature were significantly more impactful parameters, compared to the bulkier phosphines, making stereoselective control more difficult (entries 1-3). Overall, the trend for obtaining better desired stereoselectivity and yield for electron deficient phosphines is as followed: (1) decreased temperature results in higher stereoselectivity; (2) decreased time results in higher stereoselectivity at the sacrifice of yield, especially at 30°C. The observed trend for electron deficient phosphines created a dilemma for the current system employed, and with no evident alternatives, other solvents were explored instead. Changing to DCE proved incredibly beneficial in acquiring higher stereoselectivity without sacrificing yield, although it is not currently known why. It is likely due to altering the kinetics of the reaction due to the relative water solubility of each solvent. This is suggested by experimental evidence, as increasing the temperature when employing DCE showed little impact on stereoselectivity up to 80°C (entries 4, 6-8).

Table 3.5: Reaction Condition Optimization for Electron-Poor Phosphines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>NMR Yield (E:Z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65</td>
<td>THF</td>
<td>24</td>
<td>87% (41:59)</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>THF</td>
<td>24</td>
<td>83% (39:61)</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>THF</td>
<td>8</td>
<td>44% (26:74)</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>DCE</td>
<td>24</td>
<td>52% (19:81)</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>MeCN</td>
<td>24</td>
<td>99% (57:43)</td>
</tr>
<tr>
<td>6</td>
<td>40</td>
<td>DCE</td>
<td>24</td>
<td>72% (20:80)</td>
</tr>
<tr>
<td>7</td>
<td>50</td>
<td>DCE</td>
<td>24</td>
<td>99% (21:79)</td>
</tr>
<tr>
<td>8</td>
<td>80</td>
<td>DCE</td>
<td>8</td>
<td>98% (36:64)</td>
</tr>
</tbody>
</table>

From there, a small electron deficient phosphine scope was developed (Scheme 3.8). It was found that increasing the total fluorine substituents on the phosphine generally lead to lower yields and stereoselectivity (phosphines \textbf{3.2d}, \textbf{3.2e}, \textbf{3.2f}, \textbf{3.2i}). Although aryl
fluorides are often electron withdrawing due to the inductive effect, it was found that greater fluoride contribution resulted in electron donating effects (3.2e, 3.3b, 3.4a). Additionally, phosphine 3.2f and triethylphosphite proved to be too electron poor to perform the alkyne reduction. Honing in on the scope of electronics needed to facilitate an efficient stereoselective reaction, the mono-derivatized phosphine 3.2g was examined. Only a marginal increase in stereoselectivity was obtained employing 3.2g, and yield was significantly diminished. Despite 3.2g being too electron-poor to result in a high yielding reaction for these conditions, it is likely that the yield can be improved for this phosphine with slight modifications to the reaction conditions.

Scheme 3.8: Electron-Poor Phosphine Scope
3.3 Future Goals

Although this research illustrated that the stereoselective phosphine-mediated reduction of ynones can be achieved through either path of phosphine steric s or electronics, much work is ongoing towards reaching a general method that can be applied towards all substrates, as well as developing a phosphine scope that incorporates both parameters. Furthermore, a phosphine containing an electron withdrawing mono-substituent at the ortho-position, incorporating both parameters simultaneously, would lead to further mechanistic insight. Expanding even further, the role that substrate electronics and steric s play within either system are not well defined. It was found that the choice of solvent significantly influences the kinetics of the reaction, and work is still ongoing to determine the exact nature of the solvent dependent stereoselectivity, with the next logical step being the incorporation of a phase transfer catalyst.

3.4 Experimental Section

3.4.1 General

Air and moisture sensitive reactions were carried out in flame-dried glassware under nitrogen. All other reactions were setup in 8 mL oven-dried glass vials under an ambient atmosphere. Unless otherwise indicated, reagents and materials were obtained from commercial suppliers and used without further purification. Analytical TLC was performed with 0.25 mm silica gel F plates with a 254 nm indicator. Purification of products was achieved by column chromatography on Sorbtech silica gel (40-60 µm), with the indicated solvents.
NMR spectra were measured on a JEOL 400 MHz (ECS-400) Nuclear Magnetic Resonance spectrometer. For CDCl₃ solutions the chemical shifts are reported as parts per million (ppm) referenced to residual protium or carbon of the solvents; CDCl₃ δ ¹H (7.26 ppm) and CDCl₃ δ ¹³C (77.0 ppm). Coupling constants are reported in Hertz (Hz).

Characterization data for ¹H-NMR spectra are reported as followed: chemical shift (ppm, s = singlet, d = doublet, dd = doublet of doublets, t = triplet, td = triplet of doublets, q = quartet, m = multiplet), and integration. Infrared spectra were recorded on a Perkin Elmer FTIR Spectrum II spectrometer, and are reported in wavenumber (cm⁻¹) and relative intensity (br = broad, vw = very weak, w = weak, s = strong, vs = very strong, sh = shoulder).

3.4.2 Experimental Procedure

General Procedure 1: Preparation of Ynone Substrates (3.1a-3.1b):

Procedure adapted from the literature. Added to a flame-dried Schlenk flask, a solution of phenylacetylene (1.0 equiv.) and dry THF (0.25 M) was cooled to 0°C under nitrogen. n-BuLi (1.1 equiv.) was added dropwise, and the reaction solution was stirred for 1 hr at this temperature. The corresponding aldehyde (1.5 equiv.) was added dropwise, and the reaction was allowed to warm to rt. The reaction solution was quenched with DI water after 4 hr, extracted with EtOAc, and dried over MgSO₄. The solvents were removed under reduced pressure to give the crude alcohol product to which DCM (0.25 M) and
MnO₂ (10 equiv) were added and the solution was stirred at rt and in the dark for two hr. The reaction solution was filtered over celite, solvents were removed, and the crude product was purified via column chromatography on silica gel with hexanes/EtOAc (4:1) and concentrated to afford ynone 3.1a-3.1b.

1-Phenylpent-1-yn-3-one (3.1a): Product isolated as a clear, yellow oil (352.1 mg, 2.226 mmol, 89%). ¹H-NMR (400MHz, CDCl₃) δ 7.59-7.56 (m, 2H), 7.48-7.43 (m, 1H), 7.40-7.36 (m, 2H), 2.73-2.68 (q, J = 8 Hz, 2H), 1.23-1.20 (d, J = 8 Hz, 3H).

4-Methyl-1-phenylpent-1-yn-3-one (3.1b): Product isolated as a light golden oil (672.7 mg, 3.906 mmol, 78%). ¹H-NMR (400MHz, CDCl₃) δ 7.60-7.57 (m, 2H), 7.48-7.44 (m, 1H), 7.41-7.37 (m, 2H), 2.82-2.71 (m, 1H), 1.28-1.26 (d, J = 8 Hz, 6H).

General Procedure 2: Preparation of phosphines (3.2a-3.2g)

Procedure performed according to the well-known Grignard reaction. To a flame-dried Schlenk flask, a solution of aryl bromide (0.1 equiv.), dry THF (0.25 M), magnesium (1.5 equiv.), and an iodide crystal were added at rt. The solution was stirred and heated to
45°C, and after the reaction solution initiated, the remaining solution of aryl bromide (0.90 equiv.) in dry THF (0.6 M) was added dropwise over 20-60 min. The reaction solution was stirred for 2 h, cooled to 0°C, and the phosphorus electrophile (0.95 equiv.) was added dropwise. The reaction solution was allowed to warm to rt, and stirred for 6 hr. The reaction solution was quenched with DI water, extracted with DCM, and dried over MgSO₄. The solvents were removed under reduced pressure, the crude product was purified via column chromatography on silica gel with hexanes/Et₂O (60:1) and concentrated to afford the phosphine.

![Diagram of 3.2a](image)

**Diphenyl(o-tolyl)phosphane (3.2a):** Product isolated as a white solid (4.475 g, 16.19 mmol, 81%). ¹H-NMR (400MHz, CDCl₃) δ 7.36-7.22 (m, 12H), 7.12-7.08 (t, J = 8 Hz, 1H), 6.80-6.77 (m, 1H), 2.41 (s, 3H).

![Diagram of 3.2b](image)

**(2,6-Dimethylphenyl)diphenylphosphane (3.2b):** Product isolated as a clear, viscous oil (733.9 mg, 2.528 mmol, 98%). ¹H-NMR (400MHz, CDCl₃) δ 7.37-7.23 (m, 11H), 7.10-7.07 (m, 2H), 2.22 (s, 6H).
(2,3-Dimethylphenyl)diphenylphosphane (3.2c): Product isolated as a white solid (1.3247 g, 4.5624 mmol, 91%). $^1$H-NMR (400MHz, CDCl$_3$) δ 7.36-7.27 (m, 10H), 7.17-7.15 (d, $J = 8$ Hz, 1H), 7.03-6.99 (t, $J = 8$ Hz, 1H), 6.65-6.62 (m, 1H), 2.36 (s, 3H), 2.31 (s, 3H).

(4-Fluorophenyl)diphenylphosphane (3.2d): Product isolated as a white solid (760.3 mg, 2.713 mmol, 96%). $^1$H-NMR (400MHz, CDCl$_3$) δ 7.35-7.26 (m, 12H), 7.06-7.02 (t, $J = 8$ Hz, 2H).

(2,4-Difluorophenyl)diphenylphosphane (3.2e): Product isolated as a clear, viscous oil (1.312 g, 4.399 mmol, 66%). $^1$H-NMR (400MHz, CDCl$_3$) δ 7.38-7.29 (m, 10H), 6.83-6.79 (m, 3H).
(Perfluorophenyl)diphenylphosphane (3.2f): Product isolated as a yellow solid (649.6 mg, 1.8442 mmol, 92%). $^1$H-NMR (400MHz, CDCl$_3$) $\delta$ 7.44-7.36 (m, 10H).

Diphenyl(4-(trifluoromethyl)phenyl)phosphane (3.2g): Product isolated as a yellow solid (1.173 g, 3.551 mmol, 70%). $^1$H-NMR (400MHz, CDCl$_3$) $\delta$ 7.75-7.69 (m, 1H), 7.57-7.55 (d, $J = 8$ Hz, 2H), 7.38-7.32 (m, 1H).

**General Procedure 3: Preparation of phosphines (3.2h-3.2i)**

Procedure performed according to the well-known Grignard reaction. To a flame-dried Schlenk flask, a solution of aryl bromide (0.15 equiv.), dry THF (0.25 M), metal magnesium (2.5 equiv.), and an iodide crystal was added at rt. The solution was stirred and heated to 45°C, and after the reaction solution initiated, the remaining solution of aryl bromide (1.90 equiv.) in dry THF (0.6 M) was added dropwise over 20-60 min. The reaction solution was stirred for 2 h, cooled to 0°C, and the phosphorus electrophile (1.0 equiv.) was added dropwise. The reaction solution was allowed to warm to rt, and stirred
for 6 hr. The reaction solution was quenched with DI water, extracted with DCM, and dried over MgSO₄. The solvents were removed under reduced pressure, the crude product was purified via column chromatography on silica gel with hexanes/Et₂O (60:1) and concentrated to afford the phosphine.

**Phenyldi-o-tolylphosphane (3.2h):** Product isolated as a white solid (1.16 g, 3.98 mmol, 44%). ¹H-NMR (400MHz, CDCl₃) δ 7.38-7.36 (m, 4H), 7.31-7.24 (m, 5H), 7.12-7.08 (m, 2H), 6.78-6.75 (m, 2H), 2.42 (s, 6H).

**Bis(4-fluorophenyl)(phenyl)phosphane (3.2i):** Product isolated as a clear, viscous oil (490.9 mg, 1.646 mmol, 91%). ¹H-NMR (400MHz, CDCl₃) δ 7.36-7.35 (m, 3H), 7.31-7.25 (m, 6H), 7.07-7.03 (m, 4H).

**General Procedure 4: Preparation of Tris(4-fluorophenyl)phosphane (3.4a)**

Procedure performed according to the well-known Grignard reaction. To a flame-dried Schlenk flask, a solution of p-fluoro bromobenzene (0.15 equiv.), dry THF (0.25 M),
metal magnesium (3.5 equiv.), and an iodide crystal was added at rt. The solution was stirred and heated to 45°C, and after the reaction solution initiated, the remaining solution of p-fluoro bromobenzene (2.90 equiv.) in dry THF (0.6 M) was added dropwise over 20-60 min. The reaction solution was stirred for 2 h, cooled to 0°C, and PCl₃ (1.0 equiv.) was added dropwise. The reaction solution was allowed to warm to rt, and stirred for 6 hr. The reaction solution was quenched with DI water, extracted with DCM, and dried over MgSO₄. The solvents were removed under reduced pressure, the crude product was purified via column chromatography on silica gel with hexanes/Et₂O (60:1) and concentrated to afford 3.2j as a white solid (509.9 mg, 1.6123 mmol, 85%). ¹H-NMR (400MHz, CDCl₃) δ 7.67-7.61 (m, 2H), 7.27-7.20 (m, 4H), 7.20-7.15 (m, 2H), 7.07-7.03 (m, 4H).

**General Procedure 3: Synthesis of (Z)-alkene products:**

![Chemical structure](image)

To an 8 mL reaction vial was added phosphine (0.95 equiv.), the corresponding substrate (1.0 equiv, 0.15 mmol), DI water (55 equiv.), and dry THF (0.15 M). The solution was heated to 30°-80°C and stirred over 2-24 hr. The solvents were removed under reduced pressure, and the crude residue was analyzed via ¹H-NMR spectroscopy to acquire the yield and (E)//(Z)-ratio.
4. Triphenylphosphine Catalyzed Formal [3 + 3] Cycloaddition of Ynones and Nitrones to Construct Dihydro-1,2-Oxazines

4.1 Project Scope

Substituted heterocyclic compounds such as indoles, lactones, pyridines, and pyrroles are highly regarded in the realm of synthetic chemistry due to their reactivity, but can be difficult to prepare. One such class of heterocycles are the oxazines, not naturally occurring in nature and difficult to obtain using current synthetic methodologies. Oxazines feature a heterocyclic six-membered ring containing one oxygen atom and one nitrogen atom. Specifically, 1,2-oxazines contain adjacent nitrogen and oxygen atoms and have one, two, or zero alkenes (Figure 4.1). This structural motif is found in few naturally existing compounds, but holds pharmacologic potential and synthetic opportunities arriving from the cleavage of the N-O bond. This ring cleavage leads to 1,4-amino alcohols which can be further converted to numerous other useful compounds. Additionally, 1,2-oxazines could be exploited as scaffolds in the development of non-natural pharmaceuticals. Despite these merits, methodologies for constructing 1,2-oxazines are relatively lacking; existing methods generally are expensive and/or rely on transition metal catalysts. For example, the reaction of an α,β-unsaturated aldehyde with a nitrone, catalyzed by an N-Heterocyclic carbine (NHC) catalyst, yields a tetrahydro-1,2-oxazine (Scheme 4.1).
Following the recent success of the phosphine-catalyzed formal [3 + 3] cycloaddition of ynones and azomethines \(^\text{33}\) (see Scheme 1.13), a triphenylphosphine-catalyzed formal [3 + 3] cycloaddition of ynones and nitrones to construct dihydro-1,2-oxazines was proposed (Scheme 4.2). The reaction begins with the addition of PPh\(_3\) to the ynone, providing the zwitterionic intermediate I. Intermediate I is subjected to a proton transfer, facilitated by either a protic solvent, or through an intermolecular exchange, producing the enolate II. The enolate nucleophilically adds to the electrophilic nitrone, generating intermediate III. The negatively charged oxygen then undergoes an intramolecular umpolung addition to achieve intermediate IV. An additional proton transfer and elimination of triphenylphosphine yields the dihydro-1,2-oxazine product.
4.2 Results and Discussion

To test the hypothesis, 4-phenylbut-3-yn-one 2.4d and DPN were chosen as the standard substrates, with PPh₃ acting as the catalyst. Initially, the reaction was evaluated at either 30 or 50°C, employing catalytic triphenylphosphine (20 mol%) with both aprotic and protic solvents (Table 4.1) (see scheme 4.3). To our dismay, none of the six protic or aprotic solvents evaluated provided enough product to purify or definitively analyze. Particularly, column chromatography proved to be difficult, as it was realized that DPN decomposed during the reaction, indiscriminate of solvent polarity or proticity. The nitrone decomposition was further supported by GC-MS and ¹H-NMR spectroscopy. Moreover, a
known side reaction, a phosphine-free [3 + 2] cycloaddition, obtained through the reaction of 2.4d and DPN resulting in 4.3, without the participation of triphenylphosphine, was found. However, due to the harsher conditions typically necessary for the [3 + 2] annulation (Scheme 4.3), it is seemingly less competitive under the mild conditions used; only a small amount of this product was observed under our conditions. The five-membered ring is formed through a concerted addition of the oxygen from dpn to the electrophilic β-carbon of 2.4d, as the α-carbon of 2.4d bonds to the electrophilic carbon of DPN, constructing the annulated product 4.3.

**Table 4.1: Reaction Screening Table**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (hr)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₂OH</td>
<td>30</td>
<td>4</td>
<td>Decomp. + (4.3)</td>
</tr>
<tr>
<td>2</td>
<td>CH₂OH</td>
<td>50</td>
<td>4</td>
<td>Decomp. + (4.3)</td>
</tr>
<tr>
<td>3</td>
<td>CH₃CH₂OH</td>
<td>30</td>
<td>4</td>
<td>Decomp. + (4.3)</td>
</tr>
<tr>
<td>4</td>
<td>IPA</td>
<td>30</td>
<td>4</td>
<td>Decomp. + (4.3)</td>
</tr>
<tr>
<td>5</td>
<td>DCM</td>
<td>30</td>
<td>4</td>
<td>Decomp. + (4.3)</td>
</tr>
<tr>
<td>6</td>
<td>DCM</td>
<td>50</td>
<td>4</td>
<td>Decomp. + (4.3)</td>
</tr>
<tr>
<td>7</td>
<td>DCE</td>
<td>30</td>
<td>4</td>
<td>Decomp. + (4.3)</td>
</tr>
<tr>
<td>8</td>
<td>DCE</td>
<td>30</td>
<td>4</td>
<td>Decomp. + (4.3)</td>
</tr>
<tr>
<td>9</td>
<td>DCE</td>
<td>50</td>
<td>16</td>
<td>Decomp. + (4.3)</td>
</tr>
<tr>
<td>10</td>
<td>MeCN</td>
<td>30</td>
<td>4</td>
<td>Decomp. + (4.3)</td>
</tr>
<tr>
<td>11</td>
<td>MeCN</td>
<td>50</td>
<td>4</td>
<td>Decomp. + (4.3)</td>
</tr>
</tbody>
</table>

**Scheme 4.3: [3 + 2] Annulation**
Compound 4.3 was observed throughout the initial screenings. However, due to the lack of desired product formation, 2.4d was tested for its electrophilic ability to achieve annulation with methyl acrylate in the presence of triphenylphosphine (Scheme 4.4).\textsuperscript{79} This control reaction yielded 4.2, observed via crude \textsuperscript{1}H-NMR spectroscopy, corroborating the capability of 2.4d to undergo intramolecular umpolung addition granted a suitable electrophile.

\textit{Scheme 4.4: Methyl Acrylate [3 + 2] Control Reaction}

![Scheme 4.4: Methyl Acrylate [3 + 2] Control Reaction](image)

Particularly troublesome was the instability of DPN within all examined reaction conditions. It was found through flash chromatography and GC-MS that DPN decomposes into several compounds throughout the reaction, one of which appeared to be aniline. Because of the consistent decomposition of the nitrone, regardless of solvent, a Lewis acid was implemented in an effort to stabilize the oxygen (Figure 4.2). The addition of a Lewis acid offered the additional benefit of providing an enhanced electrophilic species.

\textit{Figure 4.2: Lewis Acid Charge Stability}

![Figure 4.2: Lewis Acid Charge Stability](image)

Although implementing a Lewis acid gave a mixture of inseparable products, 4.1 was detected via crude \textsuperscript{1}H-NMR spectroscopy. This evidence suggested that the incorporation of a Lewis acid was critical to the reaction and resulted in significantly less DPN decomposition. The reaction was then evaluated with stoichiometric amounts of
phosphine in hopes of increasing the total yield to obtain a definitive characterization of the product, while screening various solvents (Table 4.2).

In THF, zinc chloride was capable of preventing the decomposition of nitrone at the elevated temperature of 50°C (entry 9). Both toluene and THF resulted in significantly more product at either temperature than DCE. Moreover, it was noticed that at 30 or 50°C, the use of toluene resulted in no formation of 4.3 (entries 6 and 8). This suggests toluene could be a good solvent for an uncontested synthetic pathway. In the case of the more polar, aprotic solvent acetonitrile, insufficient product formation resulted in the inability to characterize the reaction mixture, though reasons for this are not yet known (entry 5). The protic solvent isopropanol failed to generate any desired product; however, this is largely due to the very low solubility of triphenylphosphine in isopropanol at low temperatures (entry 4).

### 4.3 Conclusions

Overall, the still unoptimized conditions suggest the need for a protic solvent or additive capable of promoting a hydrogen transfer. However, because isopropanol was not a viable candidate, n-butanol, a solvent mixture, or the inclusion of another proton source

---

**Table 4.2: Stoichiometric Condition Screening**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>PPh₃ (mol%)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DCE</td>
<td>30</td>
<td>20</td>
<td>Decomp.+4.1+4.3</td>
</tr>
<tr>
<td>2</td>
<td>DCE</td>
<td>50</td>
<td>20</td>
<td>Decomp.+4.3</td>
</tr>
<tr>
<td>3</td>
<td>DCE</td>
<td>30</td>
<td>100</td>
<td>Decomp.+4.1+4.3</td>
</tr>
<tr>
<td>4</td>
<td>IPA</td>
<td>30</td>
<td>100</td>
<td>Decomp.</td>
</tr>
<tr>
<td>5</td>
<td>MeCN</td>
<td>30</td>
<td>100</td>
<td>Decomp.+4.1+4.3</td>
</tr>
<tr>
<td>6</td>
<td>Toluene</td>
<td>30</td>
<td>100</td>
<td>Decomp.+4.1</td>
</tr>
<tr>
<td>7</td>
<td>THF</td>
<td>30</td>
<td>100</td>
<td>(4.1)+4.3</td>
</tr>
<tr>
<td>8</td>
<td>Toluene</td>
<td>50</td>
<td>100</td>
<td>Decomp.+4.1</td>
</tr>
<tr>
<td>9</td>
<td>THF</td>
<td>50</td>
<td>100</td>
<td>(4.1)+4.3</td>
</tr>
</tbody>
</table>
should be explored. Based on the previous results, employing toluene as a solvent with an acid additive such as phenol would be a logical next step. Even after implementation of a Lewis acid, DPN persisted in creating obstacles to find optimal reaction conditions for the formal [3 + 3] cycloaddition. Because dpn decomposition caused difficulties within the flash column chromatography purification process, alternative methodologies were explored (unused nitrone led to decomposition on silica). Unfortunately, purification techniques have proved laborious and difficult. Alternatively, a nitrone both more stable and electrophilic could provide a more efficient reaction while solving decomposition problems inherent in utilizing DPN.

Preliminary progress demonstrated the preparation of a dihydro-1,2-oxazine by a phosphine-catalyzed [3 + 3] annulation reaction, which is, to the best of our knowledge, the first of its kind. In the future: (1) reaction conditions should be further optimized, with utilization of a solvent or additive capable of facilitating a hydrogen transfer; and (2) a viable method of purification established. Subsequently, a substrate scope may then be realized. If successful, mild reaction conditions and an inexpensive organocatalyst would be featured qualities.

4.4 Experimental Section

4.4.1 General

Air and moisture sensitive reactions were carried out in oven-dried glassware under an ambient pressure of nitrogen in a Unilab glovebox, or positive pressure of dry nitrogen. Similarly, air-sensitive liquids and solutions were transferred in glovebox via syringe. Reactions were stirred using Teflon-coated magnetic stir bars, and elevated temperatures
were maintained using programmed temperature controlled silicone oil baths. Organic solutions were concentrated using a Buchi rotary evaporator followed by a Schlenk line vacuum pump. Acetonitrile, 1,2-dichloroethane, isopropanol, tetrahydrofuran, and toluene were distilled and degassed prior to use. Synthetic reagents were purchased from Aldrich and Alfa Aesar, and used without further purification. Analytical TLC was performed with 0.25 mm silica gel F plates with a 254 nm indicator. The TLC plates were visualized by short wave ultraviolet light, and optionally treated with potassium permanganate stain followed by mild heating. Purification of products was achieved by column chromatography on Sorbtech silica gel (40-60 µm), with the indicated solvents.

NMR spectra were measured on a JEOL 400 MHz (ECS-400) Nuclear Magnetic Resonance spectrometer. Characterization data for $^1$H-NMR spectra are reported as followed: chemical shift (ppm, referenced to TMS; s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet), and integration. Infrared spectra were recorded on a Perkin Elmer FTIR Spectrum II spectrometer, and are reported in wavenumber (cm$^{-1}$) and relative intensity (br = broad, vw = very weak, w = weak, s = strong, vs = very strong, sh = shoulder). GC-MS analysis was performed on an Agent Technologies 7890A gas chromatography instrumentation tandem with an Agent Technologies 5975C inert XL MSD with triple axis detector.

### 4.4.2 Abbreviations

DCE = 1,2-dichloroethane; MeCN = acetonitrile; IPA = isopropanol

DPN = N, alpha-diphenyl nitrene

### 4.4.3 Experimental Procedure
Synthesis of 6-benzylidene-2,3-diphenyl-1,2-oxazinan-5-one

In an 8 mL vial, dpn (20.6-24.7 mg, 0.104-0.125 mmol), PPh$_3$ (5.05-8.75 mg, 0.0193-0.0334 mmol), zinc chloride (18.0 mg, 0.132 mmol), and 4-phenyl-3-butyn-2-one (14.14-17.50 mg, 0.0981-0.1214 mmol) were dissolved in solvent (0.6-1.0 mL). The reaction solution was stirred and heated to 30-50°C either for 4 hr or overnight. The resulting solution was concentrated via solvent evaporation, and the crude product was purified via column chromatography (Hexanes/EtOAc 15:1 to 8:1) or submitted for crude $^1$H-NMR spectroscopy.

Synthesis of methyl-3-benzylidene-4-oxo-cyclopentane-1-carboxylate

To a Schlenk flask, 2.4d (1 equiv., 0.1 mmol), methyl acrylate (1 equiv.), and PPh$_3$ (0.2 equiv.), phenol (0.2 equiv.), and DCE were added under nitrogen. The reaction solution was stirred and heated to 50°C for 4 hr. The reaction solution was then concentrated under vacuum, and the crude product was characterized via $^1$H-NMR spectroscopy.
5. 1,3-Amino Alcohol One-Pot Synthesis Through an Iron-Catalyzed Borrowing Hydrogen Strategy

5.1 Introduction

5.1.1 The Catalytic Borrowing Hydrogen Strategy

A “borrowing hydrogen strategy” is one in which the combination of transfer hydrogenation with one or multiple intermediate reactions arrives at more complex molecules without the necessity for individual separation or isolation. The basis for this concept is that a hydrogen atom from a donor molecule will be stored by a catalyst to be relinquished during a concluding hydrogenation step. This strategy is generally contingent on three steps: (1) dehydrogenation via catalyst; (2) an intermediate reaction(s) induced by the increased reactivity of the unsaturated system; and (3) hydrogenation of the unsaturated species by the hydride containing catalyst (Scheme 5.1). The borrowing hydrogen strategy has been employed for a variety of synthetic methodologies. An example of the utility of this strategy is the ruthenium-catalyzed synthesis of \( \gamma \)-butyrolactones from 1,2-diols and malonates (Scheme 5.2). This process is initiated through the dehydrogenation
of 1,2-diols by a ruthenium pincer catalyst forming 1,2-hydroxyketones and ruthenium hydride. The hydroxyketone undergoes a Knoevenagel reaction with the malonate to form an unsaturated intermediate species that is subsequently reduced by the ruthenium hydride, regenerating the catalyst. The desired γ-butyrolactone is formed from a subsequent base-catalyzed annulation.

Scheme 5.2: Borrowing Hydrogen Example

5.1.2 Iron Cyclopentadienone Complexes: A Historical Perspective

Metal-catalyzed redox processes, such as hydrogenations, are vital synthetic transformations that have been known for decades. Current research has sought more environmentally friendly redox processes, some of which have been applied industrially. This focus has been long directed towards tuning the reactivity of the metal center by means of altering the electronic and steric character of the ligands.
Shvo’s catalyst is a cyclopentadienone-ligated ruthenium complex that is air-stable and commercially available. Although dimeric in its precatalytic form, when exposed to significant heat and H₂ gas, Shvo’s catalyst dissociates into two catalytically active monomeric forms (Scheme 5.3).

Scheme 5.3: Shvo’s Catalyst

These monomers consist of a ruthenium hydride species, and a coordinatively unsaturated dicarbonyl ruthenium complex. The monomeric form containing a vacant coordination site rapidly adds a hydride for occupancy. Also noteworthy, both bridging hydrogen atoms dissociates to the same monomer upon dissociation. As a result, the ruthenium hydride monomer exists in the (+2) oxidation state, while the coordinatively unsaturated ruthenium complex exists in in the zero oxidation state. When not under hydrogen pressure, the ruthenium(0) monomeric form is catalytically capable of performing a H₂ abstraction, creating a scenario where the catalytic species of higher formal oxidation state operates as a reducing agent, while the ruthenium(0) catalytic species can perform oxidations.

For example, Shvo’s catalyst dehydrogenated alcohols to the corresponding aldehydes in the presence of hydrogen acceptors (Table 5.1). These aldehydes then can further undergo a subsequent Tishchenko-style oxidative coupling to form the ester
products. Shvo’s catalyst has also been employed for the hydrogenation of alkynes, alkenes, and carbonyls, as well as the oxidation of alcohols and amines.84

Historically, noble metals (primarily 2nd and 3rd row transition metals) have dictated the field of homogenous catalysis. More recently, however, significant effort has been expensed towards utilizing cheaper and more abundant first row transition-metal analogues, specifically iron.85 Iron cyclopentadienone complexes were discovered in 1953 by Reppe and Vetter; however, it was not until the 1990s that Knölker and Pearson explored their functionality.86-87 They established a method for the oxidative decoordination of the iron metal center and successfully isolated the first iron hydride hydroxycyclopentadienyl complex via a Hieber-type reaction (Scheme 5.4).

### Scheme 5.4: Formation of Cyclopentadienyl Iron Complex

5.1.3 Redox Catalysis Through Iron Cyclopentadienone Complexes

Casey and Guan first explored the catalytic activity of these Knölker type catalysts in 2007, when they showed the reduction of various ketones, an aldehyde, and an imine, in moderate to good yields, utilizing hydrogen gas for catalyst regeneration (Scheme 5.5).88 Through this and other reports, a redox reactivity profile was developed for these Knölker-

---

**Table 5.1: Tishchenko Oxidation via Shvo’s Catalyst**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Total Yield</th>
<th>Ester</th>
<th>Aldehyde</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(CH\textsubscript{2})\textsubscript{6}CH\textsubscript{3}</td>
<td>93%</td>
<td>91%</td>
<td>2%</td>
</tr>
<tr>
<td>2</td>
<td>(CH\textsubscript{2})\textsubscript{2}CH\textsubscript{3}</td>
<td>98%</td>
<td>97%</td>
<td>1%</td>
</tr>
<tr>
<td>3</td>
<td>(CH\textsubscript{2})\textsubscript{2}(CH\textsubscript{2})\textsubscript{2}</td>
<td>95%</td>
<td>94%</td>
<td>1%</td>
</tr>
<tr>
<td>4</td>
<td>(CH\textsubscript{2})\textsubscript{6}CH\textsubscript{3}</td>
<td>76%</td>
<td>73%</td>
<td>3%</td>
</tr>
<tr>
<td>5</td>
<td>C\textsubscript{6}H\textsubscript{5}</td>
<td>96%</td>
<td>93%</td>
<td>3%</td>
</tr>
<tr>
<td>6</td>
<td>4-methyl-(C\textsubscript{6}H\textsubscript{5})</td>
<td>99%</td>
<td>86%</td>
<td>13%</td>
</tr>
</tbody>
</table>
Scheme 5.5: Knölker Catalyst Hydrogenations

Starting with benchtop-stable pre-catalysts, either hydrogen addition or the oxidative decoordination of a single CO ligand yields active forms of the catalyst in equilibrium. In the case of the iron hydride complex, the reduction of polarized double bonds is permitted based on the relative acidity of the hydroxyl group on the cyclopentadienyl ring. In the scenario where the coordinatively unsaturated iron(0) complex exists, hydrogen abstraction from alcohols is tolerated based on the Lewis basicity of the cyclopentadienone ligand.\(^8\)
The selective decoordination of a CO ligand from an iron cyclopentadienone catalyst may be achieved through an *in-situ* oxidative decomplexation using trimethylamine N-oxide (Scheme 5.7).\(^9\) In this process, the N-oxide reacts with a CO that is coordinated to the iron center to produce CO\(_2\) and trimethyl amine, producing a vacant coordination site. In 2012, Funk developed a new analogue pre-catalyst, in which a thermally labile acetonitrile ligand can produce the necessary vacant active site at...
Funk’s work allowed for a more benchtop stable, thermally labile pre-catalyst, and an increased reactivity profile for Knölker-type catalysts. Additionally, this thermally labile pre-catalyst has been computationally shown to dissociate, as well as experimentally in our lab at 65°C.

Hydrogenation is generally achieved through two strategies, direct hydrogenation via hydrogen gas, or transfer hydrogenation through a non-H₂ source. Both the transfer hydrogenation of carbonyls and imines, and alcohol dehydrogenations, by means of an iron cyclopentadienone catalyst, have illustrated equal effectivity utilizing the solvent as a hydrogen source or sink. These reaction types are often desirable due to the practicality and mild nature of the reaction. Funk demonstrated these transfer hydrogenation and dehydrogenation reactions for a variety of aldehydes, ketones, and secondary alcohols (Scheme 5.9).
5.1.4 **Intramolecular Hydrogenation Through a Borrowing Hydrogen Strategy via Iron Catalysis**

Intramolecular hydrogenation has many advantages. While a hydrogen accepting or donating solvent can provide the means for catalytic turnover, an intramolecular approach facilitates a much more efficient chemical reaction. In addition to the provisions of high atom economy and less side-product formation, the reaction is ultimately redox neutral.

After the examination of a reactivity profile for these iron cyclopentadienone complexes, a few methods have illustrated their catalytic utility when implemented within a borrowing hydrogen strategy. The seminal example of this was in 2013, with the alkylation of ketones with alcohols.\(^9\) In this report, an alcohol is dehydrogenated into the corresponding aldehyde, initiating a base-catalyzed aldol condensation reaction through an enolate intermediate. (Scheme 5.10). This aldol condensation reaction produces the corresponding \(\alpha,\beta\)-unsaturated carbonyl, susceptible to reduction by the iron hydride formed upon dehydrogenation.

Another way this borrowing hydrogen strategy has been utilized is through the formation of benzyl amines starting from benzyl alcohols and either
primary or secondary amines. Expanding the scope of benzyl alcohols capable of oxidation via Knölker-type catalysts, the resulting aldehyde undergoes imine condensation (Scheme 5.11). The formed imine intermediate is then reduced by the iron hydride to afford a secondary or tertiary amine in moderate to good yields.

### Scheme 5.11: Benzyl Amine Formation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>PPh3 (mol%)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DCE</td>
<td>30</td>
<td>20</td>
<td>Decomp. + (4.1)+(4.3)</td>
</tr>
<tr>
<td>2</td>
<td>DCE</td>
<td>50</td>
<td>20</td>
<td>Decomp. + (4.1)+(4.3)</td>
</tr>
<tr>
<td>3</td>
<td>DCE</td>
<td>30</td>
<td>100</td>
<td>Decomp. + (4.1)+(4.3)</td>
</tr>
<tr>
<td>4</td>
<td>IPA</td>
<td>30</td>
<td>100</td>
<td>Decomp.</td>
</tr>
<tr>
<td>5</td>
<td>MeCN</td>
<td>30</td>
<td>100</td>
<td>Decomp. + (4.1)+(4.3)</td>
</tr>
<tr>
<td>6</td>
<td>Toluene</td>
<td>30</td>
<td>100</td>
<td>Decomp. + (4.1)</td>
</tr>
<tr>
<td>7</td>
<td>THF</td>
<td>30</td>
<td>100</td>
<td>(4.1)+(4.3)</td>
</tr>
<tr>
<td>8</td>
<td>Toluene</td>
<td>50</td>
<td>100</td>
<td>Decomp. + (4.1)</td>
</tr>
<tr>
<td>9</td>
<td>THF</td>
<td>50</td>
<td>100</td>
<td>(4.1)+(4.3)</td>
</tr>
</tbody>
</table>

### 5.1.5 1,3-Amino Alcohols: Applicability and Challenges

Amino alcohol syntheses have been well documented due to their structural motifs being found in numerous naturally occurring and medicinal compounds. In contrast to the various methods for stereoselectively preparing 1,2-amino alcohols, fewer methodologies exist for accessing the related 1,3-amino alcohols; harsh reaction conditions and/or 2nd and 3rd row transition metal catalysts are typically employed. It is even more difficult to stereoselectively produce these 1,3-amino alcohols. Commonly, the Mannich reaction is used; however, this does not produce the amino alcohol directly (Scheme 5.12). Instead, a subsequent reduction of the resulting β-amino carbonyl compound must take place.

### Scheme 5.12: 1,3-Amino Alcohol Formation Through a Mannich Reaction

A technique utilized for directly...
achieving a stereoselective 1,3-amino alcohol synthesis is through intramolecular C-H amination; however, strong oxidants still must be used (Scheme 5.13).\textsuperscript{99,100} As such, inexpensive and mild techniques to generate stereoselective 1,3-amino alcohols have been a topic of extensive research.

\subsection*{5.2 Project Scope}

Based on reports that utilized a borrowing hydrogen strategy with the Knölker-type catalysts, an intramolecular, redox neutral strategy was proposed for synthesizing 1,3-amino alcohols via a “one-pot” Mannich reaction (Scheme 5.14). Thermal ligand dissociation of the iron catalyst allows for the dehydrogenation of a benzyl alcohol. A secondary amine nucleophilically adds to the resulting aldehyde through either a base or acid catalyzed condensation, affording an electrophilic imine susceptible to nucleophilic addition by the aryl ketone (Mannich reaction). It is worth noting that both the aldehyde formed from the dehydrogenation and the ketone must simply have one set of \(\alpha\)-hydrogens for singular nucleophilic additions to control any product selectivity. Once the Mannich base is formed, the iron hydride catalyst performs the hydrogenation to arrive at the 1,3-amino alcohol.
The methodology prescribed, unfortunately, is somewhat restrictive due to the Mannich reaction. For example, the alcohol utilized must be benzyl alcohol (or derivatives) in order to achieve transfer hydrogenation or dehydrogenation; moreover, reports have indicated that electron withdrawing substituents on the aryl alcohol increase the reactivity of dehydrogenation.\textsuperscript{83} Because the dehydrogenation must occur fast enough to avoid nucleophilic aldol addition of the amine to the ketone, electron-donating derivatives of benzyl alcohol are not optimal. Additionally, considerations must be made to prevent the resulting aldehyde from being reduced back to the corresponding benzyl alcohol; therefore, imine formation must be efficient to trap the aldehyde and push the equilibrium forward. These considerations exist for each component of the Mannich reaction; as such, the proposed model substrates are electronically neutral with the exception of the amine to avoid the use of aniline (Scheme 5.14). Generally, the Mannich
reaction operates more efficiently under acid catalyzed conditions, so $p$-TsOH was used. When choosing a solvent, attention must be given to ensure the avoidance of solvent promoted hydrogen transfer process, a criterion in which methanol meets. Additionally, polar, protic solvents help stabilize the Mannich base formation, even more so than polar, aprotic solvents such as DMSO.

### 5.3 Results and Discussion

Initially, Mannich base formation was optimized with the intent of forming product as fast as conditions would allow. This was done largely in part of facilitating the effectiveness of the aldehyde trap, but also would decrease undesired side-product formation, mainly aldol condensation (Table 5.2). It was found that methanol at 80° C afforded the fastest imine turnover with good yield.

#### Table 5.2: Mannich Base Optimization

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time (hr)</th>
<th>Temp. (°C)</th>
<th>Acid Equiv</th>
<th>A$^a$ (%)</th>
<th>B$^b$ (%)</th>
<th>Product$^a$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>i-PrOH</td>
<td>30</td>
<td>65</td>
<td>0.5</td>
<td>74</td>
<td>4</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>DCE</td>
<td>6</td>
<td>65</td>
<td>1.5</td>
<td>38</td>
<td>20</td>
<td>23</td>
</tr>
<tr>
<td>3</td>
<td>MeOH</td>
<td>22</td>
<td>65</td>
<td>0.5</td>
<td>5</td>
<td>23</td>
<td>49</td>
</tr>
<tr>
<td>4</td>
<td>DCE/MeOH (1:1)</td>
<td>8</td>
<td>65</td>
<td>1.0</td>
<td>17</td>
<td>13</td>
<td>46</td>
</tr>
<tr>
<td>5</td>
<td>DCE/MeOH (1:1)</td>
<td>9</td>
<td>80</td>
<td>1.0</td>
<td>4</td>
<td>N/A</td>
<td>93</td>
</tr>
<tr>
<td>6</td>
<td>MeOH</td>
<td>9</td>
<td>80</td>
<td>0.5</td>
<td>0</td>
<td>14</td>
<td>79</td>
</tr>
</tbody>
</table>

$^a$ $^1$H-NMR yields in crude mixture using TCE as the internal standard.
Next, the Mannich base was evaluated for its ability to effectively be hydrogenated by the iron catalyst (Table 5.2). Using IPA as a sacrificial hydrogen donor, it was found that the Mannich base could undergo the desired hydrogenation in good yields over the course of 24 h. Additionally, it showed catalytic turnover for the catalyst employing a thermally labile ligand even at 65°C, suggesting synergy between the time needed for catalytic turnover and the time needed for Mannich base formation.

Table 5.3: Reduction of Mannich Bases

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>Fe cat. 2 (10 mol%)</th>
<th>IPA, 80°C, 24h</th>
<th>R1</th>
<th>R2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>quantitative yield</td>
<td></td>
<td>Ph</td>
<td>Ph</td>
</tr>
<tr>
<td>OH HN</td>
<td>PMP</td>
<td>99%</td>
<td></td>
<td>Br</td>
<td>OH HN</td>
</tr>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>94%</td>
<td></td>
<td>MeO</td>
<td>87%</td>
</tr>
</tbody>
</table>

After this preliminary work, “one-pot” 1,3-amino alcohol reaction conditions were explored (Table 5.4). Initially, toluene was utilized to examine the interactions between the catalyst and the system used for Mannich base formation because of the solubility of the iron catalyst in toluene (entry 1). Because of the observed imine formation, the catalyst could efficiently dehydrogenate benzyl alcohol; however, in this case, p-anisidine was used and the electron donating methoxy group from the amine proved to be too electron donating for the imine to be susceptible to nucleophilic attack, evident by the reduction of acetophenone instead of Mannich base formation. Employing a new solvent system and higher temperature showed promise of 1,3-amino alcohol formation (entry 3); however, no
conditions screened ultimately afforded substantial or reliable product formation. This was partially due to reaction competition with aldol condensation, but more significantly impacted by the inability to efficiently form imine (entries 2-6). Although Mannich base formation occurred readily when employing stoichiometric amounts of benzaldehyde, \( p \)-bromoaniline was found to be too electrophilic to efficiently trap the aldehyde in this system once formed. Because of this, most of the aldehyde formed converted to the \( \alpha,\beta \)-unsaturated carbonyl, reduced ketone, or most likely, reduced to benzyl alcohol as the result of an idle catalyst.

**Table 5.4: One-Pot Synthesis of a 1,3-Amino Alcohol**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (hr)</th>
<th>Conc. (M)</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>Product(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^b)</td>
<td>Toluene</td>
<td>65</td>
<td>48</td>
<td>0.1</td>
<td>35%</td>
<td>0%</td>
<td>19%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>MeOH/DCE (1:1)</td>
<td>80</td>
<td>72</td>
<td>0.2</td>
<td>0%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>MeOH</td>
<td>80</td>
<td>72</td>
<td>0.2</td>
<td>1%</td>
<td>1%</td>
<td>7%</td>
<td>0%</td>
<td>35%</td>
</tr>
<tr>
<td>4</td>
<td>MeOH</td>
<td>80</td>
<td>72</td>
<td>0.5</td>
<td>3%</td>
<td>3%</td>
<td>5%</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>5</td>
<td>MeOH</td>
<td>90</td>
<td>72</td>
<td>0.2</td>
<td>&lt;1%</td>
<td>2%</td>
<td>&lt;1%</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>6(^c)</td>
<td>MeOH</td>
<td>80</td>
<td>72</td>
<td>0.4</td>
<td>1%</td>
<td>2%</td>
<td>2%</td>
<td>1%</td>
<td>2%</td>
</tr>
</tbody>
</table>

\(^a\) \(^1\)H-NMR yields in crude mixture

\(^b\) \( p \)-Anisidine used as amine

\(^c\) 50% of catalyst added after 24 hr
5.4 Conclusion

Unfortunately, a barrier exists between the temperature needed to catalytically promote redox reactions and the temperature needed to overcome the competitive synthetic pathway problems contributed by the Mannich reaction. Because of this, the approach of the current system cannot successfully or consistently achieve Mannich base formation. Future work would need to find alternatives to overcome this barrier, ones more suitable for these catalytic conditions.

5.5 Experimental Section

5.5.1 General

Air and moisture sensitive reactions were carried out in flame-dried glassware under nitrogen. All other reactions were setup in 8 mL oven-dried glass vials under an ambient atmosphere. Unless otherwise indicated, reagents and materials were obtained from commercial suppliers and used without further purification. Analytical TLC was performed with 0.25 mm silica gel F plates with a 254 nm indicator. Purification of products was achieved by column chromatography on Sorbtech silica gel (40-60 µm), with the indicated solvents.

NMR spectra were measured on a JEOL 400 MHz (ECS-400) Nuclear Magnetic Resonance spectrometer. For CDCl₃ solutions the chemical shifts are reported as parts per million (ppm) referenced to residual protium or carbon of the solvents; CDCl₃ δ¹H (7.26 ppm) and CDCl₃ δ¹³C (77.0 ppm). Coupling constants are reported in Hertz (Hz). Characterization data for ¹H-NMR spectra are reported as followed: chemical shift (ppm, s = singlet, d = doublet, dd = doublet of doublets, t = triplet, td = triplet of doublets, q =
quartet, m = multiplet), and integration. Infrared spectra were recorded on a Perkin Elmer FTIR Spectrum II spectrometer, and are reported in wavenumber (cm$^{-1}$) and relative intensity (br = broad, vw = very weak, w = weak, s = strong, vs = very strong, sh = shoulder).

5.3.2 Abbreviations

$p$-TsOH = $p$-toluene sulfonic acid; IPA = isopropanol; MeOH = methanol; EtOH = ethanol; MeCN = acetonitrile

5.3.3 Experimental Procedure

General Procedure 1: Preparation of Mannich Base

To an oven-dried 8 mL reaction vial was added benzaldehyde (1.0 equiv., 0.2 mmol), $p$-bromoaniline (1.0 equiv.), acetophenone (3.0 equiv, 0.10 mmol), MeOH (2.0 M), $p$-TsOH (1.0 equiv.) and molecular seives. The solution was heated to 80°C and stirred for 2-30 hr. The reaction solution was filtered, the solvents were removed under reduced pressure, and the crude residue was analyzed via $^1$H-NMR spectroscopy to obtain yield. TCE was used as the internal standard.
General Procedure 2: Preparation of Amino Alcohols

To an oven-dried 8 mL reaction vial was added benzyl alcohol (1.5 equiv.), p-bromoaniline (1.5 equiv.), aceophenone (1.0 equiv, 0.10 mmol), MeOH (0.25 M), iron catalyst (0.1 equiv.), p-TsOH (0.5 equiv.) and molecular sieves under nitrogen. The solution was heated to 80°C and stirred for 48-72 hr. The reaction solution was quenched with H2O, extracted with EtOAc, and dried over MgSO4. The solvents were removed under reduced pressure, and the crude residue was analyzed via 1H-NMR spectroscopy to obtain yield. TCE was used as the internal standard.
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Appendix